Organic Reactions

Organic Reactions

VOLUME I

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PREFACE

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manula furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. Volume I of Organic Reactions is a collection of twelve chanters, each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in Organic Syntheses they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such commonted and references however, because of the very return of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed. Nevertheless, the

investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the book will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the index have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the index.

The success of this publication, which will appear periodically in volumes of about twelve chapters, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

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CHAPTER 1

THE REFORMATSKY REACTION

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GENERAL CONSIDERATIONS

The reaction which takes place between a carbonyl compound such as an aldehyde, a ketone, or an ester and an α -haloester in the presence of zinc is commonly known as the Reformatsky reaction.\(^1\) It represents an extension of the reactions of carbonyl compounds with a dialkylzinc or an alkylzinc halide, but possesses the advantage that the isolation of the organozinc compound is unnecessary. The process creates a new carbon-carbon linkage and appears to involve the following steps.\(^2\)

1. Formation of an organozine halide.

$$X - C - CO_2R + Zn \rightarrow X - Zn - C - CO_2R$$
[1]

(X represents Cl, Br, I; R is an alkyl group.)

2. Addition to the carbonyl group of the aldehyde or ketone.

$$\begin{array}{c|c}
 & XZnO \\
 & & | & | \\
 -C - O + X - Zn - C - CO_2R \rightarrow -C - C - CO_2R \\
 & & | & | & | \\
 & & & \Pi
\end{array}$$
[2]

3. Decomposition by dilute acids.

$$\begin{array}{c|c} XZnO & OH \\ \hline -C - C - CO_2R + HX \rightarrow -C - C - CO_2R + ZnX_2 & [3] \\ \hline \end{array}$$

Thus an aldehyde or a ketone leads to a β -hydroxyester (III) as the final product. Subsequent or simultaneous dehydration may produce an unsaturated ester.

When an ester is used instead of an aldehyde or ketone the addition product IV is formed.

$$\begin{array}{c|c} & XZ_{n}O \\ \hline -C=O+X-Z_{n}-C-CO_{2}R & \to & \begin{array}{c|c} & & \\ &$$

Reformatsky, Ber., 20, 1210 (1887).

² Reformatsky, J. prakt. Chem., 54, 469 (1896).

If this addition complex is stable, then the product obtained by hydrolysis of the reaction mixture is a θ -ketnester.

If the addition product decomposes spontaneously, the β -ketoester (V) may again be the final product.

$$\begin{array}{c|c} OZnX & O & \\ \hline OZnX & C & CO_2R \\ \hline OR' & CO_2R \\ \hline OR' & OR' \\ \end{array}$$

If the keto group in this ketoester is reactive and an excess of the organozine halide (I) is present, further reaction may take place as in equation 2 above.

Evidence for the existence of the organizinc halide (I) as an intermediate was provided by G. Dain, who isolated and analyzed the following compounds.

Three addition products corresponding to the complex II were also obtained

These complexes, therefore, parallel the intermediates formed in the well-known reactions involving the Grignard reagent or similar organometallic haldes and carbonyl compounds. Indeed, magnesium may be used in place of rinc (p. 16), and apparently the intermediate complexes are analogous. Grignard reagents cannot be prepared from a-haloesters and magnesium alone; hence the Reformatsky reaction offers a pro-

Dain, J. Russ, Phys. Chem. Soc., 28, 593 (1896).

cedure by which the equivalent of a Grignard reagent from an α -haloester is available for synthetic work. In the subsequent discussion these intermediates will not always be written and only the reactants and main products will be shown. It is to be understood, however, that the steps shown above are always involved.

Relative Reactivities of Reagents. The order of reactivity of carbonyl compounds in the Reformatsky reaction is RCHO > R_2 CO > RCO₂- C_2 H₅. The order of reactivity of the haloacetates is ICH₂CO₂C₂H₅> BrCH₂CO₂C₂H₅ > ClCH₂CO₂C₂H₅. The α -chloroacetic esters often react slowly or not at all, and the α -iodoesters are not readily available. Consequently, most Reformatsky reactions have been carried out with the α -bromoesters. Esters containing a secondary or tertiary α -chlorine atom are much more reactive than the corresponding primary derivatives and in some cases are reported to give good yields. The three types of α -bromoesters appear to react equally well.

Side Reactions. Various side reactions may be expected whenever the Reformatsky reaction is carried out. The intermediate organozinc halide may add to the carbonyl group of the α -haloester used as the reagent; for example, Hann and Lapworth α -have reported that zinc and ethyl bromoacetate react to produce ethyl γ -bromoacetoacetate.

$$\begin{array}{c} \text{OZnBr} \\ \text{2BrCH}_2\text{CO}_2\text{C}_2\text{H}_5 \div \text{Zn} \rightarrow \text{BrCH}_2\text{C} - \text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \\ \text{OC}_2\text{H}_5 \\ \downarrow \\ \text{BrCH}_2\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5 \div \text{C}_2\text{H}_2\text{OZnBr} \end{array}$$

Since aldehydes and ketones possess far greater carbonyl reactivity than the ester group, this side reaction is not important when aldehydes and ketones are used. Moreover, its significance may be minimized by using an excess of the bromoester and adding the latter in successive portions.

A common side reaction is the coupling of the haloester by the zinc.

$$\begin{array}{c} CH_2CO_2C_2H_5 \\ 2BrCH_2CO_2C_2H_5 \div Zn \rightarrow ZnBr_2 \div \\ CH_2CO_2C_2H_5 \end{array}$$

When aliphatic aldehydes or aliphatic or alicyclic ketones are used these may undergo aldolization under the influence of the zinc salts.

⁴ Hann and Lapworth, Proc. Chem. Soc., 19, 189 (1903).

Not only does aldolization use up the aldehyde or ketone, but also the dehydration of the aldol produces water which decomposes the intermediate organization halide (I).

$$X-Z_{B}-\overset{1}{\underset{\longrightarrow}{C}}-CO_{2}R+H_{2}O\rightarrow H-\overset{1}{\underset{\longrightarrow}{C}}-CO_{2}R+Z_{B}(OH)X$$

The organozine compound may also induce enclization.

$$RCOCH_1R + C_1H_1CHC_0C_2H_1 \rightarrow R-C=CHR + CH_1(CH_1)_1CO_1C_1H_1$$

Subsequent hydrolysis of the bromozine enolate regenerates the original ketone. This reaction accounts for the recovery of appreciable amounts of the starting material and the presence of ethyl n-butyrate among the reaction products.

THE USE OF THE REFORMATSKY REACTION

From a synthetic point of view the Reformately reaction not only constitutes a method for preparing β -hydrovyesters, and the corresponding unsaturated esters and acids but also is a valuable procedure for lengthening the carbon chain by two carbon atoms. The chain may be hranched on the α , β , or α and β -carbon atoms by proper choice of reactants. Since the product contains the carbothoxy group, it is possible by a proper sequence of reactions to repeat the chain-lengthening process. Several examples have been chosen to illustrate the utility of the condensation and to point out the part played by the Reformatsky reaction in a synthetic sequence.

⁴ Newman, J. Am. Chem. Soc., 65, 870 (1940).

Lengthening the Carbon Chain. Lengthening the Carbon Chain of an Aldehyde without Branching the Chain.

The process may be repeated, leading to R(CH₂)₄CHO.

Lengthening the Carbon Chain with Branching on the α -Carbon Atom.

Use of the sequence of reactions outlined under the first example to convert the ester group into an aldehyde group leads to the synthesis of branched-chain esters of the following type.

^{*} The dehydration of β -hydroxyesters frequently produces a mixture of $\alpha.\beta$ - and $\beta.\gamma$ unsaturated esters (see p. 12). Both may be reduced catalytically to the saturated ester

Lengthening the Carbon Chain with Branching on the \$\beta\$-Carbon Atom.

R-CHCH₂CO₂C₂H₃

The ester group of the final product may be converted into a keto group by the following reactions.

Repetition of these sequences of reactions leads to the preparation of a second type of branched-chain ester.

R[-CH--CH₂--]_a--CO₂C₂H₆

The nature of the R' group is determined by the starting ketone and the zinc alkyl used in converting the acid chloride into the final ketone. The R' groups may be alike or different.

Lengthening the Carbon Chain with Branching on Both α- and β-Carbon Atoms.

The nature of the R and R' groups is determined by the ketone and that of the R" group by the haloester.

Lengthening the Carbon Chain with Double Branching on the α -Carbon Atom.

Oceasionally, hydroxyesters of this type may be dehydrated to β, γ unsaturated esters which can then be reduced to the saturated esters. However, conversion of these α, α -disubstituted- β -hydroxyesters to the saturated esters is usually best effected by refluxing with phosphorus and hydriodic acid.

These five general types of reactions therefore constitute methods for synthesizing straight-chain and branched-chain hydroxyesters and unsaturated and saturated esters and acids.

Whether or not the Reformatsky reaction is the best method for lengthening a given earbon chain depends on a number of factors. For example, cinnamic acid may be prepared by any of the following reactions.

Perkin reaction

Yield, %*

$$\begin{array}{c} \text{C}_{e}\text{H}_{b}\text{CHO} + (\text{CH}_{3}\text{CO})_{2}\text{O} \xrightarrow{\text{CH}_{3}\text{CO}_{2}\text{Na}} \text{C}_{e}\text{H}_{b}\text{CH} = \text{CHCO}_{2}\text{H} & 80 \\ \text{Claisen condensation} \\ \text{C}_{e}\text{H}_{b}\text{CHO} + \text{CH}_{3}\text{CO}_{2}\text{C}_{2}\text{H}_{b} \xrightarrow{\text{NaOC}_{2}\text{H}_{5}} \text{C}_{e}\text{H}_{b}\text{CH} = \text{CHCO}_{2}\text{C}_{2}\text{H}_{b} & 74 \\ \text{C}_{e}\text{H}_{b}\text{CHO} + \text{CH}_{3}\text{CO}_{2}\text{C}_{2}\text{H}_{b} & \text{C}_{e}\text{H}_{b}\text{CH} = \text{CHCO}_{2}\text{H}_{b} & 72 \\ \text{Reformatsky reaction} & \text{OH} \\ \text{C}_{e}\text{H}_{b}\text{CHO} + \text{BrCH}_{2}\text{CO}_{2}\text{C}_{2}\text{H}_{b} & \xrightarrow{\text{Zn}} & \text{C}_{e}\text{H}_{e}\text{CH} = \text{CH}_{2}\text{CO}_{2}\text{C}_{2}\text{H}_{b} & 64 \\ & -\text{H}_{2}\text{O} \\ \text{C}_{e}\text{H}_{e}\text{CH} = \text{CHCO}_{2}\text{C}_{2}\text{H}_{b} & 57 \\ \text{C}_{e}\text{H}_{e}\text{CH} = \text{CHCO}_{2}\text{H}_{b} & 55 \\ \text{Knoevenagel condensation} \\ \text{C}_{e}\text{H}_{e}\text{CHO} + \text{CH}_{2}(\text{CO}_{2}\text{H})_{2} & \xrightarrow{\text{NH}_{3}} & \text{C}_{e}\text{H}_{e}\text{CH} = \text{C}(\text{CO}_{2}\text{H})_{2} \\ & \downarrow -\text{CO}_{2} \\ \end{array}$$

C.H.CH=CHCO.H

80

^{*}These figures represent the over-all yields of the products shown, based on benzaldchyde

On the basis of yields alone, the Knoevenagel or Perkin condensation would be preferred for preparing einnamie acid. From an economic point of view, the reaction chosen would depend on the relative cost of the reagents and the time involved in the preparation. The Reformatsky reaction would not be selected.

However, in the synthesis of an unsaturated acid with branching on the β-carbon atom (C₆H₂C=CHCO₂H) from the ketone (C₆H₅COR)

the Reformatsky is the only method of these four which will give good yields; the Perkin reaction fails to take place, the Claisen condensation leads to an entirely different product (a 1.3-diketone), and the Knoevenagel condensation gives low yields for small R groups and fails if R is large. Branching of the chain on both α and β -carbon atoms can be accomplished only by the Reformatsky method.

Synthesis of Arylacetic Acids. The Reformatsky reaction is also particularly well adapted to the synthesis of arylacetic acids or their seters. Thus, ketones such as 1-tetralone or 1-ketotertahydrophenanthrene¹ give hydroxyesters which are readily dehydrated to dihydroxyelacetic esters. The latter may be easily dehydrogenated to the aromatic compounds.

$$\bigcap_{0}^{CH_{2}CO_{1}C_{1}H_{1}} \bigoplus_{0}^{CH_{2}CO_{2}C_{1}H_{1}} \bigoplus_{0}^{CH_{2}CO_{2}C_{2}H_{1}} \bigoplus_{0}^{CH_{2}CO_{2}C_{2}H_{1}$$

Synthesis of \$-Xetoesters. Very few applications of the Reformatsly reaction to the synthesis of \$\theta\text{-ketoesters}\$ by reactions involving the carbonyl group of an exter are recorded. Bthyl \$\gamma\text{-bromoacetoacetate}\$ is formed by the action of zine or magnesium on ethyl bromoacetate. It hamel \$\gamma\text{-reported 50%}\$ yields of ethyl \$\gamma\text{-bhoroacetoacetate}\$ by the action of amalgamated inagnesium on ethyl chloroacetate. Ethyl \$\gamma\text{-cthyl-re-thoxyace-toacetate}\$ has been prepared in 10 to 33% yields from ethyl ethory.

Bachmann, J. Org. Chem., 3, 434 (1938).

⁴ Hamel, Bull. soc. chim., [4] 29, 390 (1921); Stolle, Ber., 41, 954 (1908).

acetate and ethyl bromoacetate 7 by using amalgamated zinc. If ethyl α -bromopropionate is used, the α -methyl derivative is produced.⁸

$$\begin{array}{c} O \\ C_2H_5OCH_2C-OC_2H_5 + BrCH_2CO_2C_2H_5 \xrightarrow{Z_{\mathbf{D}(Hg)_s}} \\ OZnBr \\ C_2H_5OCH_2C-CH_2CO_2C_2H_5 \\ \downarrow \\ OC_2H_5 \\ \downarrow \\ \downarrow \\ \downarrow \\ C_2H_5OCH_2C-CH_2CO_2C_2H_5 \end{array}$$

Ethyl 3,4-diketoadipate 9 has been obtained from ethyl oxalate, ethyl chloroacetate, and zinc.

$$\begin{array}{c|c} CO_2C_2H_5 & COCH_2CO_2C_2H_5 \\ & + 2ClCH_2CO_2C_2H_5 & \xrightarrow{Z_n} & COCH_2CO_2C_2H_5 \\ CO_2C_2H_5 & COCH_2CO_2C_2H_5 \end{array}$$

On the other hand, ethyl α -bromoisobutyrate is reported to react with ethyl oxalate to form ethyl α,α -dimethylmalate.¹⁰ It is evident that reduction takes place during this reaction.

$$\begin{array}{c|c} \text{CO}_2\text{C}_2\text{H}_5 & \text{HOCHCO}_2\text{C}_2\text{H}_5 \\ \downarrow & \downarrow & \text{CO}_2\text{C}_2\text{H}_5 \\ \end{array} \xrightarrow{\text{CO}_2\text{C}_2\text{H}_5} + (\text{CH}_3)_2\text{C} - \text{CO}_2\text{C}_2\text{H}_5 \xrightarrow{\text{Zn}} \begin{array}{c} \text{HOCHCO}_2\text{C}_2\text{H}_5 \\ \downarrow & \downarrow & \text{(CH}_3)_2\text{C} - \text{CO}_2\text{C}_2\text{H}_5 \end{array}$$

The chief product from ethyl formate, ethyl chloroacetate, and zinc is ethyl trimesate.¹¹ Ethyl formate undergoes the normal Reformatsky reaction to produce the aldehydoester which then trimerizes.

$$\begin{array}{c} O \\ O \\ C_2H_5O - C - H + CICH_2CO_2C_2H_5 \xrightarrow{Z_n} C_2H_5O - C - CH_2CO_2C_2H_5 \\ \hline \\ CO_2C_2H_5 \\ \hline \\ C_2H_5O_2C \xrightarrow{C} CO_2C_2H_5 \xrightarrow{H} \\ \end{array}$$

⁷ Sommelet, Bull. soc. chim., [4] 29, 553 (1921); Compt. rend., 154, 706 (1912).

⁸ Johnson, J. Am. Chem. Soc., 35, 582 (1913); Johnson and Chernoff, J. Am. Chem. Soc., 35, 585 (1913); 36, 1742 (1914).

⁵ Fittig and Daimler, Ber., 20, 202 (1887).

¹⁰ Rassow and Bauer, Ber., 41, 963 (1908).

¹¹ Reformatsky, J. Russ. Phys. Chem. Soc., 30, 280 (1898); J. prakt. Chem., 54, 477 (1896).

With ethyl α-bromopropionate, the presence of the α-methyl group in the intermediate aldehydoester prevents the trimerization. Hence a second Reformatsky reaction occurs leading to ethyl 2,4-dimethyl-3hydroxyglutarate.12 Ethyl a-bromoisobutyrate, ethyl formate, and zinc react in a similar fashion to produce ethyl 2,2,4,4-tetramethyl-3-hydroxyelutarata 13

Oxidation * of the \$-hydroxyesters, obtained by the Reformatsky reaction on aldehydes, by means of the calculated amount of chromic acid in glacial acetic acid as the solvent, produces \$6-ketoesters in low vields (30-50%).

RCHOHCH-CO-CH- Cros RCOCH-CO-CH-

Thus, B-ketoesters with no a-substituents may be obtained. This is useful since the Claisen condensation of esters (other than ethyl acetate) yields α-substituted β-ketoesters (see Chapter 9).

DEHYDRATION OF THE 6-HYDROXYESTERS

If the temperature of the reaction mixture is high it occasionally happens that the product from the Reformatsky reaction is the unsaturated ester. However, if the reaction is run in the usual solvents, such as ether or benzene (p. 15), the chief constituent of the reaction mixture is the hydroxyester. Because of their tendency to lose water during distillation or saponification, "the β -hydroxyesters and their derivatives can sometimes be isolated in the pure state only with difficulty and in poor yields, whereas dehydration of the crude reaction mixtures leads to higher yields of the unsaturated products.

Dehydration may be accomplished by heating the \$-hydroxyester with acctic anhydride, acetic anhydride and acetyl chloride.15 fused potassium acid sulfate. 16 85% formic acid, 17 anhydrous formic acid, 5, 18, 19 zinc chloride in acetic acid,20 or sulfuric acid 21 of various strengths (20 to

^{*}See p. 22, reference 48 12 Reformatsky, Ber., 28, 3263 (1895).

¹¹ Risise, Compt. rend., 126, 1808 (1898)-

¹⁴ Schroeter, Ber., 37, 1090 (1904); 40, 1589 (1907).

¹⁵ Stoermer and Frederici, Ber., 41, 324 (1908).

¹⁴ Wallach, Ann., 365, 255 (1909). 17 Rupe, Ann., 369, 321 (1909).

¹⁸ Cook, J. Chem. Soc., 2524 (1931); Bachmann and Edgerton, J. Am. Chem. Soc., 62 2971 (1940).

¹⁸ Bergmann and Bograchov. J. Am Chem. Soc., \$2, 3017 (1940). 20 Wallach, Ann , 314, 147 (1901), Tetry, Bull. soc chun , [3] 27, 600 (1902)

¹¹ Jaworsky and Reformatsky, Ber., 35, 3633 (1902).

65%); or by refluxing a benzene solution of the β -hydroxyester with iodine, ²² acetic anhydride, acetic anhydride and sodium acetate, ²³ phosphorus pentoxide, ²⁴ phosphorus oxychloride, ^{24, 25} or thionyl chloride and pyridine. ^{24, 26} Passing dry hydrogen chloride through the β -hydroxyester at 90–100° followed by distillation is also a very satisfactory method ²⁷ (90–95% yields) of dehydration.

For many years it had been assumed that the product of the dehydration reaction was the conjugated α,β -unsaturated ester. When the β -hydroxyl group is secondary, or when an aryl group is attached to the β -carbon atom, the chief product (and in many cases the only one isolated) is, indeed, the α,β -unsaturated ester or acid.

ArCHCH₂CO₂H
$$\rightarrow$$
 ArCH=CHCO₂H \mid OH

However, when the hydroxyl group is tertiary the structure of the dehydration product is determined by the nature of the substituents. The α,β -unsaturated ester is the chief product when an aryl group or two methyl groups are attached to the β -carbon atom.

However, when one of the alkyl groups is other than methyl then both α,β - and β,γ -unsaturated esters are produced.

$$\begin{array}{c|c} R \\ RCH_2 - C - CH_2CO_2C_2H_5 \\ OH \\ \end{array}$$

$$\begin{array}{c|c} R \\ RCH_2 - C - CH_2CO_2C_2H_5 \\ RCH_2 - CH_2CO_2C_2H_5 \\ \end{array}$$

²² Hibbert, J. Am. Chem. Soc., 37, 1748 (1915).

²³ Rupe and Busolt, Ber., 40, 4537 (1907).

²⁴ Kon and Nargund, J. Chem. Soc., 2461 (1932); Phalnikar and Nargund, J. Indian Chem. Soc., 14, 736 (1937).

²⁵ Lindenbaum, Ber., 50, 1270 (1917).

²⁵ Darzens, Compt. rend., 152, 1601 (1911).

²⁷ Natelson and Gottfried, J. Am. Chem. Soc., 61, 970 (1939).

The proportion of the two isomeric esters depends on the reagent used and on the structure of the compound. The dehydration of a number of β -hydrocyseters by means of four dehydrating agents has been studied by Kon and Nargund.²⁴ The total yield of the mixture of α,β - and β,γ -unsaturated esters was 80–95%. In Table I is shown the percentage of the total product which was the α,β - unsaturated esters.

TABLE I
DESUBRATION OF S-HIDROXIESTERS

	[Perce	Percentage of α,β-Unsaturated Ester						
β-Hydroxyester	P ₂ O ₆	POCI	SOC1,	(fused) KHSO ₁				
C'H'-C-CH'CO'C'H'	39	62	53	57				
он С'н"—ссн'со:с'н" С'н"	23	68	50	63				
C,H, C,H,—O—CH,CO,C,H, OH	24	51	31	51				
C,H, CH, CH,—CHCO,C,H,	28	43	33	28				
CH*CO'C'H'	19	43	32	4.5				
CH'CO'C'H'	30	58	50	38				

It is occasionally possible to obtain either one of the isomeric dehydration products by proper choice of the experimental conditions. For example, dehydration of etbyl 1-hydroxycyclohexylactets with actic anhydride followed by saponification gives Δ'-cyclohexenylacetic acid;

if the ester is first saponified and the 1-hydroxycyclohexylacetic acid is dehydrated with acetic anhydride the chief product is cyclohexylidene acetic acid. In syntheses of saturated esters or acids it is unnecessary to separate the α,β - and β,γ -esters or acids before reduction.

Sometimes cleavage occurs as a side reaction in dchydration of β -hydroxyacids. Thus heat causes the decomposition of α -(1-hydroxy-3-methylcyclohexyl) propionic acid.¹⁶

Sulfuric acid causes the cleavage of α,α-dialkyl-β-hydroxy acids.11

$$\begin{array}{c|c} R \\ \downarrow \\ \text{CH}_3\text{CH} \longrightarrow \text{CO}_2\text{H} \xrightarrow{\text{H}_2\text{SO}_4} \text{CH}_3\text{CHO} + R_2\text{CHCO}_2\text{H} \\ \downarrow \uparrow & \downarrow \\ \text{OH} & R \end{array}$$

Hot concentrated alkalies may also cause cleavage of the molecule in certain instances.

In order to obtain the unsaturated compound and avoid this cleavage it is essential to dehydrate before hydrolyzing.^{28, 29}

SELECTIÓN OF EXPERIMENTAL CONDITIONS. PROCEDURES

In the earlier experiments,^{2, 30} the α -haloester, carbonyl compound, and zinc dust were mixed at room temperature and cooled in order to moderate the initial reaction which may cause a considerable temperature rise (60° to 120°). The mixture was allowed to stand at room temperature for periods ranging from two days to three months. After a final warming to 60–70° for two to three hours the mixture was decomposed with dilute acid. The ester was separated or extracted by a solvent, dried, and distilled in vacuum.

²⁵ Bachmann, Cole, and Wilds, J. Am. Chem. Soc., 62, 824 (1940).

²³ Bachmann and Wilds, J. Am. Chem. Soc., 62, 2086 (1940).

²⁷ Reformatsky and Plesconossoff, Ber., 28, 2838 (1895).

Control of the initial exothermic reaction may be accomplished by addition of the zinc dust in portions to the other reactants or by the use of a solvent. In most of the recent applications of the Reformatsky reaction a solvent has been employed. This permits better control of the temperature and facilitates stirring. It is essential that the surface of the zinc be kept clean. The formation of an oily product which coats the zinc may stop the reaction. By the proper selection of the solvent mixture it is often possible to keep the addition product in solution or to cause it to crystallize so that it is more readily shaken from the metal by the stirrer. The zinc may be suspended in a copper basket in order to facilitate removal of the addition compounds.

By raising the temperature to the boiling point of the solution the condensation can be effected in a much shorter time (usually one-half to three hours). A prolonged reaction time there is not the properties of the products. The solvents used have been eithyl ether, butyl ether, benzene, toluene, and xylene. A mixture of equal amounts of benzene and toluene, and the permits refluxing at temperatures between 90° and 105°, is especially advantageous when the carbonyl reagent is a ketone. Somewhat lower temperatures (70–80°) are better when an ali-patie aldelyde is employed. However, where paraformaldehyde is introduced into the reaction mixture as a source of formaldehyde, the temperature must be high enough (80–100°) to cause depolymerization.

The reagents should be pure and dry. The apparatus should also be clean and dry and protected from the moisture of the air. The observance of strictly anhydrous conditions not only improves the yield but also reduces the induction period so that the reaction usually starts immediately. If difficulty is experienced, the addition of a few crystals of iodine, a little amalgamated zine, or a very little methylmagnesium oldide may help in initiating the reaction. The copper complex of ethyl acctoacetate has been used as a catalyst. Once started, the reaction is quite vigorous. For this reason, only a small portion of the reactants should be used at the start and the bulk of the materials should be added gradually. Since c-haloesters are lachrymators and skin irritants, precautions should be taken to avoid contact with them.

Zinc dust, zinc foil, granulated zinc, and mossy zinc have been used Variations in the quality of the zinc are responsible for differences of opinion concerning yields, catalysts, and purification procedures. It is

⁸¹ Kohler and Gilman, J. Am. Chem. Soc., 41, 683 (1919).

²⁰⁶ Nieuwland and Daly, J. Am. Chem. Soc., 53, 1842 (1931).

¹²⁶ Lipkin and Stewart, 161d., 61, 3295 (1939).

¹⁴ Kohler, Heritage, and Mselcod, Am. Chem. J., 46, 221 (1911).

desirable that the zinc be as pure as possible and have a fresh clean surface. Any of the forms of zinc may be purified by washing rapidly with 2% hydrochloric or hydrobromic acid, then with water, alcohol, acetone, and absolute ether. The zinc is then warmed in a vacuum oven at 100° for a short time and used immediately. A very active metal has been obtained by immersing 30-mesh zinc in hot (100°) concentrated sulfuric acid containing a few drops of nitric acid.²¹ After about fifteen minutes the surface becomes bright and the acid is diluted with a large volume of water. The zinc is washed with water and acetone and then dried. Zinc foil may be cleaned with sandpaper and cut into small strips.

In certain instances amalgamated zinc and a mixture of zinc dust and copper powder $^{2\alpha}$ have been used to effect the condensation. Cadmium powder and mixed cadmium-copper powder are ineffective. $^{2\alpha}$ Magnesium has also been employed in place of zinc but usually results in lower yields. For example, Zelinsky and Gutt 25 used magnesium to effect the reaction between cyclic ketones and α -bromo- and α -iodo-exters. The yields ranged from 20 to 50%, whereas other investigators report that when zinc was employed the yields were 56 to 70% for the same reactants. Kon and Nargund 24 obtained yields of 48% in the condensation of aliphatic ketones with α -chloroesters and magnesium.

Many different experimental conditions have been described in connection with the Reformatsky reaction, and inspection of the literature reveals that there is no uniformity as regards the procedures. Hence the yields shown in Tables II, III, and IV of the succeeding part do not necessarily represent the highest attainable.

Four procedures have been chosen to illustrate the best methods available at the present time. These procedures not only illustrate the use of different forms of zinc but also bring out other experimental variations. One of the first three procedures should be selected when the reactants are easily available. Procedure 1 illustrates the Reformatsky reaction on an aldehyde, and procedures 2 and 3 on ketones. If the carbonyl compound is one which does not readily undergo self-condensation in the presence of zinc salts, then higher yields can be obtained by treating it repeatedly with zinc and the α -haloester as illustrated by procedure $\frac{1}{2}$. This method is especially advantageous when the ketone is available in only small amounts.

Ethyl β-Phenyl-β-hydroxypropionate.²² In a clean, dry 500-cc. three-necked flask fitted with a mechanical stirrer, a 250-cc. separatory funnel,

²⁴ Fieser and Johnson, J. Am. Chem. Soc., 62, 575 (1940).

²¹ Zelinsky and Gutt, Ber., 25, 2140 (1902); Willstätter and Hatt, Ann., 418, 148 (1919).

²⁴ Hauser and Breslow, Org. Syntheses, 21, 51 (1941).

and a reflux condenser, the upper end of which is protected by a calcium chloride drying tube, is placed 40 g. (0.62 mole) of purified zine dust or granulated zinc. A solution of 83 5 g. (0 50 mole) of othyl bromogeotate and 65 g. (0.61 mole) of benzaldehyde in 80 cc. of dry benzene and 20 cc. of alsolute ether is placed in the separatory funnel. Along 15 cc. of this solution is added to the zine and the flask is warmed until the reaction starts. The mixture is then stirred and the rest of the solution introduced at such a rate that gentle reflixing occurs, about one hour being required. Reflexing is continued for an additional half hour. The flask is then cooled in an ice both and the contents poured into 300 cc. of ice-cold 10% sulfuric acid with vicorous stirring. The acid layer is drawn off and the benzene solution extracted twice with 50-cc, portions of ice-cold 5% sulfuric acid. The bearene solution is washed once with 25 cc. of cold 10% aqueous sodium carbonate, then with 25 cc. of cold 5% sulfuric acid, and finally with two 25-cc, portions of water. The combined acid extracts are washed with two 50-ce, portions of other, and the combined other and benzene solutions are dried with 5 c. of anhydrous magnesium sulfate or Drierite. After filtration, the solvent is removed by distillation at atmospheric pressure on a steam bath and the residue is fractionated in vacuum. The ester is collected at 151-154°/11-12 mm, or 128-132°/5-7 mm. The yield is 59-62 g. (61-64%).

Ethyl 1-Hydroxycycloherylacetate." A mixture of 800 cc. of benzene and 700 cc. of toluene with 331 g. (2 moles) of ethyl bromoacetate and 190 g. (2 moles) of cyclohexanone is prepared. To 300 cc. of this mixture in a 5-1, three-necked flask fitted with mechanical stirrer, condenser with drying tule, and dronning funnel is added 130 g. (2 moles) of rine foil which has been cleaned with sandpaper and cut in strips. A few crystals of lodine are introduced, the stirrer is started, and heat is applied by means of a boiling water bath. A vigorous reaction sets in. The remainder of the reaction mixture is now added through the dropping funnel at a rate designed to maintain gentle refluxing. Stirring is then continued for two hours. Practically all the zine dissotves. The mixture is cooled and the condensation product is decomposed with ditute sulfuric acid (sufficient to dissolve all the zine hydrovide). The benzenetoluene tayer is separated, dried over anhydrous sodium suffate, and distilled in vacuum. The product is collected at 86-89°/2 mm. The yield ranges from 219 to 278 g. (56-71%).

Ethyl a-Methyl-\$-phenyl-\$-hydroxyhutyrate." A mixture of 110 g. of acetophenone, 162 g. of ethyl a-bromopropionate, and 200 ce. of dry benzene is placed in a 500-ce. separatory funnel inserted in one opening

¹¹ Rupe, Steiger, and Fiedler, Ber., 47, 68 (1914); Burton and Shopee, J. Chem. Soc., 1160 (1935); Klortrel, J. Am. Chem. Soc., 62, 1708 (1940).

125-1255° are obtained. By reworking the mother fiquors a total yield of 85-90% may be obtained.

EXAMPLES OF THE REFORMATSKY REACTION

In the tables which follow, a number of examples of the Reformatsky, traction have been collected to indicate its applicability in synthesis. The tables are undoubtedly incomplete because the reaction frequently has been used as merely one step in a synthesis and hence may not be indexed as a Reformatsky process. As pointed out previously (p. 16), because of the wide variations in the experimental conditions employed by different investigators, the yields given are not necessarily the best obtainable. For the same trason comparisons of yields reported by different authors and often referred to different standards of purity are not significant.

Aldchrides (Table II). Alighatic and aromatic aldchydes, saturated

and unsaturated addehydes undergo the reaction easily. The traction has been reported to fail with phenolic addehydes, he but recent work by Connor 1th indicates that a reaction does take place.

Me Reformataly, J. press. Chem. \$4, 479, 477 (1497).

**Italy h Conner, private communication.

TABLE II Reformatisky Reactions on Aldehydes

Mast	KEFORMATEN LUCACITORS OF THE			
Aklehyda	a-Halocster	Product Isolated	Yield, %	Reference
110110	CH3CHPrCO ₂ C ₂ H ₈	Hydroxyester	2)-	33
110110	C ₂ 11 ₆ C1111 ₇ CO ₂ C ₂ (1 ₆	Hydroxyester	2 .	e,
110110	(CII,),CBrCO,C,II,	Hydroxyrster	8	=
110110	C11,(C11,),C1113rCO2C118	Hydroxyester	67	<u></u>
110110	C ₁ II,CBrCO ₁ C ₁ II,	Hydroxyester	99	<u>:</u>
	CII,			
110710	CCII,),CIICII BrCO,C, II,	Hydroxyester	=	Ç,
IICHO	CII3(CII2),CIIIBrCO2C2IIs	Hydroxycater	22	<u>0</u> ;
110110	(n)C,111,C1111rCO,C,113	Hydroxyester	1	ë
CII,CIIO	CIC113CO3C313	None	l	t;
C11,C110	Cittocoluico	Hydroxyester	1	=
CII3CIIO	(CII ₃) ₂ CI ₃ ·CO ₂ C ₂ II ₃	Hydroxyester	5	-15, 16
CIICIIO	CIII);CIICIIIIrCO,C,II,	Hydroxyester	1	÷
CII,CII,CIIO	CIC113CO5C118	None	1	ŧ
CI1,CI1,CI10	14C112C02C2113	Hydroxyester	30	45
C113C113C110	(CII,),CI3-CO,C,11,	Hydroxyester	55	3%1
CII3CII3CII0	(n)C3II7CIIIIrCO2C21Is	Hydroxyester	25	SĮ.
C(1,(C(1,1),C(1,0)	BrC11-CO-C-118	llydroxyester	25	Ş.
(CII _a) ₂ CIICIIO	115050511541	Hydroxyester	35	\$
(C113)2C11C11O	CHICHINCOCCIT	Hydroxyester	=	ક્ક
(CII ₃) ₂ CHCHO	(C11,)2C13rCO2C211,	Hydrovyester	58	51, 52
	CII3CIIIIrCO2C2II3	Hydroxyester	1	8
(CI15),CI1CI1,CI10	(CII3)2CI3rCO3C3118	Hydroxyester	23	27
(CII)2CIICII2CIIO	(CII.),CIICIIIN:CO.C.11,8	Hydroxyester	ì	8
CH ₃ (CH ₂) ₆ CHO	IrCII;CO;C;II;	Hydroxyester	12	18, 56

				ţ
CH3(CH2),CHO	(CIII) CBCOCCH	Hydroxyester	t	ā
CH,-CIICHO	(CII), CB-CO-C, II,	Hydroxyester	ç	23
CH-CH=CHCHO	B-CH-CO-CH	Unsaturated acid	8	21
OH-CHCHO	CIT-CHB-CO-C-II.	Unsaturated acid	8	77
OHOUS CHOICE	Or Otto Co II	W. Jenn color	ş	2
CIPCII	Chichorogram	11) Groxy tester	4	3
CH,CII—CIICHO	CHICITIP-CO-CHI	Hydroxyester	8	8
CII,CII=CIICI10	CHICH Decogni	Unsaturated acid	22	72
CHCHCHCHO	CIT-LCB-CO-C-II.	Hydroxyester	i	21.60
OHOUS CHOICE	P.CH.CO.C.II.	III december	42	12
	Denicologia	Tributovicus:	2 :	5 1
Furfural	(CH)ACISCOSCIII	Unsaturated ester	5	382
CILCIO				
	BrCH,CO,C,H,	Hydroxyester	ı	62
Ν				
CII, CII,				
CII. CII. OII.				
)				
CII-CII-CII-CIICIIO	Bellico.C.II.	Hadrowseefee	2	6
	tuiologia i	11) dioxy tager	3	20
, io				
CII.				
CH,C=CHCH,CH,C=CHCHO	BrCH.CO.C.II,	Unsaturated acid	ı	ξ
CHCHO	CONTROL	Thursday	è	; ;
OH CHO	The second	Diparturated ester	3	43
Chigoria	CCHCCCH	Uneaturated acid	S	35
Centrolia	B-Cli-Co-C-11	Hydroxyester	19	48, 64
Callacito	CILCIIB-CO,CII,	Hydroxyester	28	es
CHICHO	Can Chibroo, Can	Hydroxyester	22	S
CelleCIIO	(CII,),CB-CO,C,II,	Hydroxyester	g	2
Collectio	(CHA)-CHCITB-CO-Cat.	Tredeorgeater	2 8	3 8
	***************************************	in the second se	3	200

Norm. References 39-71a appear on p 22

haloester. The reaction follows an abnormal course with halogenated aliphatic ketones and fails with phenolic ketones. Most a.S-unsaturated ketones undergo the normal Reformatsky reaction with a haloesters of monobasic acids. However, it has been observed by Kohler, Heritage, and Macleod " that methyl bromozinemalonate adds 1.4 to benzalace-

Ketones (Table III). Aliphatic, promatic, eyelic, saturated, and unsaturated ketones have been found to undergo the reaction smoothly. In the case of a ketoester, it is the keto group which reacts with the

 C_4H_4CH = $CHCOC_4H_4$ + $BrCH(CO_2CH_4)_2$ $\xrightarrow{Z_{A}}$ C_4H_4CH -CH= CC_4H_4

bromomalonate in the presence of zinc, the only product isolated is that corresponding to 1.4-addition of the haloester to mesityl oxide. The Evidently, mesityl oxide is formed by the condensation of acetone induced

2CH₂COCH₂ -> (CH₂)₂C=CHCOCH₂

tophenone. Ethyl a-bromoisohutyrate also adds 1.4 to benzalacetophenone " in the presence of zine. When acetone is treated with methyl

 $(CH_1)_1C$ — $CHCOCH_1 + BrCH(CO_1CH_2)_2 \xrightarrow{Z_{\Delta}} (CH_2)_2C$ —CH=C— CH_3

OZnBr

CH(CO*CH*)*

OZnBr

CH(CO₂CH₃)₂

115 Iyer, J. Indian Chem. Soc., 17, 215 (1940).

by the RZnX complex.

TABLE III

Reformatsky Reactions on Ketones

	INSPONDING ALEACTIONS ON TAXABLE			
Ketono	α-Haloester	Product	Yield, %	Reference
CH.COCH.	CICH2CO2C2II6	Hydroxyester	i	-
CHICOCHI	ICH, CO, C, H,	Hydroxyester	1	-
CHICOCHI	CH3CHBrCO2CH5	Hydroxyester	39	72
CHCOCII	C214,CHCICO2CH3	Hydroxyester	33	32
CHACOCHA	C2H5CHBrCO2C2H5	Unsaturated acid	39	38a
CHCOCH	(CH3)2CBrCO2C2H5	Ilydroxyester	22	30
CII,COCII,	(CH ₃) ₂ CIICHBrCO ₂ C ₂ II ₆	Hydroxyester	20	38a
$CH_3COC_3H_7(n)$	CICII, CO, C, II,	Hydroxyester	20	38a
C,II,COC,III	CICII,CO,C,II,	Hydroxyester	87	38a
$(n)C_3II_7C0C_3II_7(n)$	CICITACOACAIL	Hydroxyester	95	38a
$(n)C_3II_7COC_3II_7(n)$	(CH ₃) ₂ CBrCO ₂ C ₂ H ₅	Hydroxyacid	1	38a
CII,COCII—CHCII,	BrCH2CO2CH3	Hydroxyester	55	73
CH ₃ COCH=C(CH ₃) ₂	BrCII,CO,C,II,	Unsaturated ester	1	7.4
CII3CO(CII=CII)2CH3	BrCH2CO2CH3	Ilydroxyester	30	73
CII3COCII=CHCII=C(CII3)2	BrCH2CO2CH3	Hydroxyester	25	73
CII3COCII=CIICII=C(CII3)2	BrCH2CO2CH3	Unsaturated ester	80	19
CH3COCII=CIICH2CII(CH3)2	BrCII2CO2C2Hs	Hydroxyester	20	75
CII3COCH=CIICH2CH(CH3)2	ICH2CO.C.II.	Hydroxyester	ı	92
CH, CII,				
CII,CII,COCII,	BrCII,CO,C,II,	IIydroxyester	1	77

	77, 78	79	22	80	32	3 63	12	2 23	22	32	32	32
	88	. 1	3	93	\$ 8	2 2	26.5	25 32	28	27	33	30
_	Unsaturated ester	Unsaturated ester	Unsaturated ester	11y droxyes ter	Hydroxyester Hydroxyester	Hydroxyester Unsaturated exter	Hydroxyester	Unsaturated ester	Hydroxyester	Hydroxyester	Unsaturated ester	Hydroxyester
	всисоси	Въспъсо,с,п,	BrCH,CO,C,H,	вси,со,с,п,	CICH-CO-C-H	CICH,CO,C,H,	BrCH,CO,C,II,	CICH,CO,C,H,	SCH-CHCCOCH.	Confedence of the	CONTROCAL	Secretary of the
"B"	CH-CHCOCH,	CH, CH, CH, CH, CHCOCH, CHCOCH, CHCOCH,	CH, CH, CH, OH —CH—CH—CHCHCH,COCH,	CH, CH, CH, CH, CH, COII, COII, COII, COII,	Catacocti, Catacocti, Catacocti,	PCHC.H.COCH.	o Clifo City COCH,	P-CH ₂ CC ₆ H ₄ CCCH ₃	p-CH3OC,H,COCH3	C.H.COC.H.	C.H.COC.H.	Norz, References 72-996 appear on p. 32

TABLE III-Continued

REFORMATSICY REACTIONS ON KETONES

Katono	α-Haloester	Product	Yield, %	Reference
C.II. COC.11:	BrCII,CO ₂ C ₂ II ₆	Hydroxyester	7.5	23
711.700.4118	11000011	Hydroxyester	ı	\mathbf{s}_{1}
Care CO C 13 Co C 1 2 C C C C C C C C C C C C C C C C C	Incil. Co.Cil.	Unsaturated ester	238	73
	BrCH3CO,CH3	Unsaturated ester	22	73
Cyclonentanone	CII,CIIIIrCO,C.11	Hydroxyester	ı	16
3-Mothylevelopentanone	13rC11gC0,Cg118	Ilydroxyester	ı	02 02
Gydolioxunono	13rC113C03C3118	Ilydroxyester	52	85
Cyclohaganono	CHACHBICOCCIUS	Hydroxyester	77	83
Cyclohexanone	C,11,C1111rCO,C,11	IIydroxyester	æ	8
Cyclohexanono	(C113), C13, C3, C2, 116	Hydroxyester	ı	83
2-Methyleveloboxanono	(CII3)2CBrCO2C2118	Hydroxyester	1	88
3-Nethyleyelohexanene	13rC112C02C2115	Ilydroxyester	ä	0;
1-Methyloyelohexanone	CII,CHBrCO,CII,	Hydroxyester	77	æ
1-Mothyloyelohexanone	C1116CHBrCO2C2116	Ilydroxyester	81	83
3-Mothylayelahoxanona	(C113), C11rC0, C;11s	Ilydroxyester	1	88
4-Methyleyelehexmone	Inclinco, Cylls	Hydroxyester	75	91
4-Mothyloyelohexanone	CII,CIIBrCO2C2116	Hydroxyester	81	16, 83
4-Mothyloyelohaxanona	C2116CHBrCO2C2116	Hydroxyester	87	. 33
4-Mathylayelohexanono	(CIII)2CIBrCO2C2118	Hydroxyester	1	83
4-Mothoxyoyolohoxunono	DrCII,CO,C,II,	Hydroxyester	99	-
çıı, Çııı,				
$\operatorname{CiI_{2}=} \Diamond - \langle - \rangle_{-10}$	BrCII,CO,C,II,	Hydroxyester	20	50

. 20	50	28	22222	.	80	
S	1 .	8	200252	1	27 10	
Hydroxyester	Hydroxyester	Ilydroxyester	Hydroxyester None None None Hydroxyester Hydroxyester Unanturnted order	Hydroxyester	Hydroxyester Unsaturated oster	
BrCH,CO,GH,	BrCH;CO,C,H,	BiCH,CO,CiTL	Brottschold, Brottschold, Brottschold, Brottschold, Brottschold, Brottschold, Brottschold,	BrCH, CO, C, H.	CICH,CO2CyH, (CH,)2CB-CO2CyH,	
CII, CII, CII,	CII,	-2	(CHL)ACO Liestin O.Metbyliestin N.Metbyliestin N.Etbyliestin N.Metbyliesetin N.Metbyliesetinide	COCHOCH,	CH,COCH,CO,C,H, CH,COCH,CO,C,H,	Norm References 72-005 appear on p. 32

TABLE III—Continued
Revormatest Reactions on Ketones

1				
Katono	n-Halocster	Product	Yield, %	Yield, % Reference
CII,COCCO,C,114	BrCH 2CO 5C311s	Unsaturated ester	25	80
COCO,C,11, COCO,C,11,	BrCII1CO,C111	Hydroxyester	Đ	00
CH ₃ O ₆ 112	BrC11,CO,C,111,	Hydroxyester	f	0
CII,30 CII,3	BrC11,C0,C11,	Hydroxyester	85-90	જુદ
O CH3.	BrCII,c0,C11,	Unsaturated acid	21	66

33 31 71b	93	16	8	va .
1 2 1	ı	£	£ .	8
Keto ester 1,4- addition Keto ester 1,4- addition Keto ester 1,4- addition	Hydroxyester	Hydroxyoster	Hydroxyester	Unaturated ester
BrCH(CO ₂ CH ₃); (CH ₃);CBrCO ₃ C ₃ H ₅ BrCH(CO ₂ CH ₃);	CH-CHB-CO-C-H.	CH,CHB-CO,C,IT,	BrcII,CO,CII,	BrCH ₂ CO ₂ CH ₄
(כווי):לייכוו—כוונספלווי פ'תיכוו—כוונספלווי פ'תיכוו—כוונספלווי	CII,	oli cer	, co, out	

Nors. References 72-935 appear on p 37.

TABLE III-Continued

REFORMATISKY REACTIONS ON KETONES

***************************************	ener.	£	ž	8	61
	- Refe				
	Yield, C. Reference	6	93	1	09
	Product	Unaturated ever	Unsaturated exter	Hydroxyester	Unsaturated ester
NEFORMATSKI MINCHISTO	a-Haloester	BrCH,CO,C;H,	BrCII,CO,CII,	BrCII,CO,CII,	BrCH,CO,CH,
	Ketone			COCIIIs	CH3C

RETONES					
26	å	#4	88	999	
89	25	13	92	9	
Unsaturated acid	Unsaturated acid	Unsaturated acid	llydroxyester	Unsaturated ester	
BrCH,CO,C,H,	Спспвсосла	Br (CH),doo,c,H,	BrCH,CO,C,H,	BrCH ₅ CO ₆ CH,	
C,H,	Catt.	Cui,	Ç-cıı,	CII,	

NOTE. References 72-935 appear on p. 32

<i>"</i>	The Target Sanda Wilder
time.	
111—Con	
TAILTH III—Continue	

1	1	THE REFO	RMATSK	y reaction
	Reforence	ਜ਼ 	900	(1042). 5 (1940). 74 (1048). 74 (1048). 505, 50, 14
	Yield, %	Ģ.	25	mnun, 4, 81 fenre, 91, 438 1160 (1897), f). Cullain, J. G Them. Soc., 7 f (1838), f, (1838), f, (1838), f, (1838), f, (1838), f, (1838), f, (1848), f, (18
PROBACTION ON TENTONES	Product	Unsafarated acid	Hydroxy ester	 at Lukey, Gallertion Greeboshw, Chem. Cammun., 4, 81 (1032). by Italicy, Gallertion Greeboshw, Chem. Soc., 71, 1180 (1807). by Perkin and Thurpe, J. Chem. Soc., 71, 1180 (1807). by Lawrenne, J. Chem. Soc., 71, 167 (1807). by Haberland, Rev., 69, 1380 (1030). by Newman, J. Am. Chem. Soc., 62, 2205 (1040). by Adamson, Marlow, and Shaonsen, and Chlam, J. Chem. Soc., 667 (1910). by Adamson, Marlow, and Shaonsen, J. Chem. Soc., 774 (1038). by Adamson, Marlow, and Shaonsen, J. Chem. Soc., 774 (1038). by Adamson, Marlow, and Hallennan, Rev., 66, 1302 (1033). by Nowman, J. Am. Chem. Soc., 60, 2047 (1038). by Horganna and Ham-therganaum, J. Am. Chem. Soc., 71 (1030). by Horganaum and Ham-therganaum, J. Am. Chem. Soc., 69, 1573 (1037).
	a-Halowler	lırGH3CO3CH3	(CH1,),CDr(CO,C311,	eth. 16, 878 Fall (1010). III, 184 (1010). (1018).
and.		Company of the state of the sta	Part of the second seco	14 (Maruff, J. Russ. Phys. Chem. Soc., 28, 501 (1800). 15 Kuhn and Hoffer, Rev., 65, 651 (1812). 16 Rupo and Lats. Rev., 36, 15 (1913). 17 Raren, Britann, Rev., 36, 15 (1913). 18 Karen, Salomon, Marf, and Walker, Reb. Chim. Ach., 15, 878 (1912). 18 Kuhn and Marris, Rev., 70, 853 (1937). 19 Kuhn and Marris, Rev., 70, 853 (1937). 19 Hellbran, Jones, Lowe, and Writht, J. Chem. Soc., 501 (1939). 19 Hellbran, Jones, Lowe, and Writht, J. Chem. Soc., 501 (1939). 19 Wallach, Ann., 347, 323 (1908). 19 Wallach, Ann., 347, 323 (1908). 10 Greenber, Ph.D. Gwels, Univ. of Ht., 1939. 10 Greenber, Ph.D. Gwels, Univ. of Ht., 1939. 11 Greenber, Ph.D. Gwels, Univ. of Ht., 1939. 11 Greenber, Ph.D. Gwels, Univ. of Ht., 1939. 12 Nyana and Omaston, J. Chem. Soc., 1778 (1932). 13 Nyana and Lindwalt, J. Am. Chem. Soc., 60, 614 (1938).

Denotitions Presented by Parent TABLE IV

Ester	Haloester	Product	Yield, %	Yield, % Reference
HCO ₂ C ₂ H ₈	CICII,CO,C,II, BrCII,CO,C,II, Br	Ehyl trimesate Ehyl trimesato	11	= %
IICO,C,IIA	CII,CIICO,CIII,	Ethyl 2,4-dimethy [-3-hydroxyglutarata	ŧ	12
nco _l c _i n, c _i n,ocn,co _l c _i n,	(OII), COO, CIII, BrOII, CO, CIII, Br	Ehyl 2,2,4,4-tetramethyl 3-hydroxyglutarata Ethyl y-ethoxyacetoacetato	1 %	£ 4.
Calliochiaco, Calli Breilico, Calli Clenico, Calli	CHISTICO, CHIL PICHICO, CHIL CICHICO, CHIL	Ethyl c-methyl-y-ethoxyacetoacetato Ethyl y-thromonectoacetato Ethyl y-chloroacetoacetato	-18	8 2 3
CO ₁ C ₂ II ₄	CICII2CO2CIII	Ethyl g.y-diketoadipato	1	6
CO ₂ C ₂ H ₄	Вг (СПа)3ССО3С3Па	Etbyl a,a-dimethylmalato	1	2
Br (CH ₃) ₂ CCO ₂ C ₂ H ₄	Br CII4)2CCO2C4II4	Ethyl isobutyrylisobutyrate	49	8

Esters (Table IV). There are relatively few examples of the Reformatsky reaction involving the ester group. The yields appear to be uniformly poor.

Substituted Amides. Lukeš⁵⁷ has obtained ethyl 1-methyl-2-pyrrolone-5-acetate in about 20% yield by treating N-methyl succinimide with ethyl bromoacetate and zinc.

$$\begin{array}{c|c} \text{CH}_2\text{--CO} & \text{CH}=\text{C}\text{--CH}_2\text{CO}_2\text{C}_2\text{H}_5\\ \hline & \text{N}\text{--CH}_3 & \xrightarrow{\text{BrCH}_2\text{CO}_2\text{C}_2\text{H}_5} & \text{N}\text{--CH}_3\\ \hline & \text{CH}_2\text{--CO} & \text{CH}_2\text{--CO} \end{array}$$

VARIATIONS OF THE REFORMATSKY REACTION

Use of Halogen Compounds Other Than α -Haloesters. Aromatic aldehydes react with β - and γ -bromo- and iodo-esters in the presence of zinc, but the yields are very low (1 to 3%). 6-Methoxy-1-tetralone reacts with ethyl β -bromopropionate in the presence of magnesium to give a 22% yield of the unsaturated acid.¹⁹¹

Certain reactive halogen compounds, other than α -haloesters, have been found to condense with aromatic aldehydes in the presence of zinc. Benzyl halides yield substituted stilbenes since the carbinols are easily dehydrated during the reaction.

$$ArCHO + Ar'CH_2X \xrightarrow{Z_2} ArCHOHCH_2Ar'$$

$$\downarrow \\ ArCH=CHAr'$$

The vinylogs of the α -haloesters undergo the Reformatsky reaction; thus p-chlorobenzaldehyde, ethyl γ -iodocrotonate, and zinc react to form the expected condensation product in 42% yield.

CHO
$$+ ICH_{2}CH = CHCO_{2}C_{2}H_{5} \xrightarrow{Z_{2}} CI$$

$$CHCH_{2}CH = CHCO_{2}C_{2}H_{5}$$

$$CI$$

$$CH = CH = CH = CHCO_{2}C_{2}H_{5}$$

tri Haberland and Heinrich, Ber., 72, 1222 (1939).

¹⁷² Fuson, Arnold. and Cooke, J. Am. Chem. Soc., 60, 2272 (1938).

TABLE V
VARIATIONS OF THE REPORATISET REACTION

Aldehyde or Ketone	Halogen Compounds	Product	Yield, 75	Reference
Canacho Canacho	CCH,CH=CHCO,CH,	None		103
CHCHO PCICHCIIO	ICH, CHECHO, CAN	II) droxyester Unsaturated ester	. E	88
p-ClC,H,CHO 6-Methoxy-1-tetralone	ICHICH CHOCOCHIA	Hydroxyester and unacturated ester Uncaturated acid	£ £	22.5
Callectio Callectio	Carrena Brchicalcocur(p)	Stillsene Sulatituted atillsene	7.5	23
P-CIC,H,CHO	BrCH,C,H,CO,CH,(p)	Substituted stillens	: 818	123
P-BrC,H,CHO P-CH,O,CC,H,CHO	BrCH, C, II, CO, CII, (p)	Substituted stillsens Substituted stillsens	182	2 2 2
Ċ	ICH;CH=CHCO;C;H;	Unsaturated ester	: 15	102
Call, COCH,	CLCHCOLC.H. ICHICHICH.COCH.	Ifydroxychloroester Ifydroxyketene	8	105

¹¹⁴ Arnold, Ph.D. thems, University of Illinois, 1937.
¹¹⁴ Fuson and Cooke, J. Am. Chem. Soc., 62, 1180 (1940).

¹⁴⁶ Darzens, Compt. rend., 201, 1374 (1035), ¹⁷⁶ Verley, Bull. soc. chim., [3] 17, 102 (1897).

methyl ketones, RCOCH₂X (X = halogen). However, Arndt and co-workers,^{3, 4, 5} and shortly thereafter Robinson and Bradley,⁶ showed that diazoketones were obtained in nearly quantitative yield when the acid chloride was added slowly to a cold solution of an excess of diazomethane. This procedure varied from that of Nierenstein, who usually added one mole of diazomethane to the acid chloride, sometimes at slightly elevated temperatures (35°). According to Arndt and co-workers and Bradley and Schwarzenbach,⁷ the following reactions take place when an acid chloride is added to diazomethane.

(a)
$$RCOCl + CH_2N_2 \rightarrow RCOCHN_2 + HCl$$

(b)
$$HCl + CH_2N_2 \rightarrow CH_3Cl + N_2$$

(c)
$$RCOCHN_2 + HCl \rightarrow RCOCH_2Cl + N_2$$

The initial reaction is the formation of the diazoketone with liberation of hydrogen chloride (a). The hydrogen chloride then reacts with a second molecule of diazomethane to form methyl chloride (b). If any of the hydrogen chloride is not destroyed in this reaction, it will react with the diazoketone to yield the ω-chloromethylketone (c). In general, where there is always an excess of diazomethane, reaction (c) takes place to a very limited extent, because the excess diazomethane reacts with the hydrogen chloride almost as fast as the hydrogen chloride is formed. However, when the reaction is run so that there is always an excess of acid chloride (by adding the diazomethane slowly to the acid chloride), some chloromethyl ketone is formed, especially at higher temperatures, although the high yields of this product obtained by Nierenstein have not been duplicated by other investigators.

With the diazoketones readily available, Arndt and Eistert ⁸ made a study of the Wolff rearrangement and showed that it was of quite general application. They pointed out that a combination of the two reactions, the formation of the diazoketone from acid chlorides and the Wolff rearrangement, constituted a new method of lengthening a carbon chain by one methylene group.

The diazoketones are believed to decompose by way of intermediates similar to those involved in the Curtius rearrangement of acid

³ Arndt, Eistert, and Partale, Ber., 60, 1364 (1927).

⁴ Arndt and Amende, Ber., 61, 1122 (1928).

⁵ Arndt, Eistert, and Amende, Ber., 61, 1949 (1928).

Robinson and Bradley, J. Chem. Soc., 1310 (1928).
 Bradley and Schwarzenbach, J. Chem. Soc., 2904 (1928).

⁴ Arndt and Eistert, Ber., 68, 200 (1935).

azides. $^{1, \ 0, \ 10, \ 11}$ The nitrogen is eliminated, and a short-lived radical is produced which rearranges to the corresponding ketene.

$$RCOCHN_2 \rightarrow N_2 + [RCOCH=] \rightarrow RCH=C=0$$

 $RCON_2 \rightarrow N_1 + [RCON=] \rightarrow RN=C=0$

In several cases the intermediate ketenes have been isolated, but ordinarily they are converted to the acids, esters, or amides by the water, alcohol, ammonia, or amine present in the reaction mixture.

RCH=C=0 + HOH
$$\rightarrow$$
 RCH₂CO₂H
+ R'OH \rightarrow RCH₂CO₂R'
+ NH₁ \rightarrow RCH₂CONH₂
+ R'NH₂ \rightarrow RCH₂CONHR'

The rearrangement of optically active diazoketones, in which the carbon atom attached to the carbonyl group was asymmetric, resulted in the formation of optically active products except in one or two instances. In II This result is similar to that observed in the rearrangement of optically active acid aides.

It is considered that the metal catalyst which is usually required for the reaction accelerates the decomposition of the diazoketone to the ketene, since in the absence of such a catalyst no rearrangement takes place and the product formed is a derivative of the ketone. Thus, if diazoacetophenone is heated with water at 70-80°, benzoylearbinol is obtained. 1°

If silver is present, rearrangement takes place and pheaplacetic acid is formed. Wolff i found that the addition of powdered silver did not catalyze the decomposition of diazoacetone in the presence of ammonia, but that the reaction was rapid if either silver oxide or silver nitrate was added. Thus, it appears that the entalyst, if it is metallic silver, must be colloidally dispersed. Arnott and Eistert i found that even with highly purified diazoketone there was always a small amount of reduction of the silver salts which could account for the production of the necessary catalyst, Powdered copper and platinum have also been used as catalysts in the rearrangement but much less frequently.

Eistert, Ber., 68, 208 (1935).

Lane, Willens, Weissberger, and Walls, J. Org. Chem., 5, 276 (1940).
 Lane and Walls. J. Org. Chem., 8, 443 (1941).

¹⁵ Schroeter, Ber., 43, 2346 (1909); 49, 2704 (1916), Standinger and Hursel, Ber., 43 2522 (1916).

THE SCOPE AND LIMITATIONS OF THE SYNTHESIS

It is apparent that by the Arndt-Eistert synthesis an acid can be converted to its next higher homolog by a three-step process. The over-all yield is ordinarily between 50 and 80%. Other well-known methods for accomplishing the same result include the following processes, which are presented in outline form.

[1]
$$RCO_2H \rightarrow RCOCl \rightarrow RCHO \rightarrow RCH_2OH \rightarrow RCH_2Br \rightarrow$$

RCH₂CN (or RCH₂MgBr) → RCH₂CO₂H

[2]
$$RCO_2H \rightarrow RCO_2C_2H_5 \rightarrow RCH_2OH \rightarrow RCH_2Br \rightarrow RCH_2CN$$

(or RCH₂MgBr) → RCH₂CO₂H

[3]
$$RCO_2H \rightarrow RCOCI \rightarrow RCOCN \rightarrow RCOCO_2H \rightarrow RCH_2CO_2H$$

The choice of the method to be used depends on several factors, such as the amount of the acid desired, the type of acid, and the over-all yields possible. Methods I and 2, which consist of more steps than the Arndt-Eistert reaction, often give lower over-all yields and require a longer working time. Method 3 generally gives poor yields of the product. The Arndt-Eistert reaction can be carried through rapidly, one day usually being sufficient for the complete synthesis, and it is thus an ideal method when only small amounts of the final product are desired. It is of interest that Eistert ¹² and Burger and Avakian ¹⁴ have worked successfully with amounts of diazoketone as large as 100 g.

Each of the three methods outlined above involves a more or less drastic reduction which may interfere with its application to a compound containing a nitro, quinone, keto, lactone, ester, or other reducible group. The Arndt-Eistert reaction involves no such step and can be used for the preparation of molecules which are sensitive to reducing agents. For example, the nitrophenylacetic acids can be prepared easily and in good yields from the nitrobenzoyl chlorides. 5. 15

$$\begin{array}{c|c} & & & \\ & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\$$

¹² Eistert, Ber., 69, 1074 (1936).

¹¹ Burger and Avakian, J. Org. Chem., 5, 606 (1949).

u Bachmann and Holmes, unpublished results.

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d-Homopilopic acid can be prepared from d-pilopic acid, the lactone ring remaining intact throughout the synthesis. 16, 16,

An illustration of the conversion of a 8,7-unsaturated acid to its homolog is the preparation of \$\textit{B-(2-methyleyclohexenyl)}\$-propionic acid from 2methyleyclohexenylacetic acid.**

A dicarbovylic acid can be converted, through its acid ester, to its next higher homolog, a process which would be difficult to accomplish by other methods. Thus, glutaric acid has been converted to adipic acid through the intermediate ester chloride.¹²

The Arndt-Eistert reaction is ideal for use on complex molecules. The reaction is carried out at moderately low temperatures so that the chances of decomposing the molecule are not as great as in some of the other syntheses. An interesting example in the synthesis of the sex hormone equilenin is the conversion of one of the intermediates to its next higher homolog in good yield (80-84%).

Preobrashenski, Poljakowa, and Preobrashenski, Ber., 68, 850 (1935).
 Poljakowa, Preobrashenski, and Preobrashenski, Ber., 69, 1314 (1936).

Plenti and Bogert, J. Org. Chem., 6, 669 (1941).
 Bachmann and Sheehan, unpublished results.

Bachmann, Cole, and Wilds, J. Am. Chem. Soc., 62, 824 (1940).

The following are some of the syntheses that have been carried out in the heterocyclic series by means of the Arndt-Eistert synthesis.

Although diazoketones have been prepared successfully from 2-,2 3-,2 and 4-pyridinecarboxylic acid 2 and from 4-quinolinecarboxylic acid,2 the Wolfi rearrangement on the diazoketones has not been reported. The complete synthesis has been carried out on N-methylpyrrole-2-carboxylic acid.22

An ingenious application of the synthesis has been made in a synthesis of papaverine. The diazoketone prepared from the acid chloride of veratric acid and diazomethane was allowed to react with homoveratrylamine to give the substituted amide of homoveratric acid, which was then cyclized and dehydrogenated to papaverine.²⁵

$$\begin{array}{c} \text{CH:} \\ \text{CH:$$

T Blicke and M. F. Zienty, J. Am. Chem. Soc., 63, 2945 (1941).

Arndt and Eistern, Ger. pat., 650,705 [C. A., 22, 595 (1935)].
 Crook and Davies, J. Chem. Soc., 1627 (1937).

Titof, Müller, and Reichstein, Helr. Chim. Acta, 20, 883 (1937).
 Winterfeld and Cosel, Arch. Pharm., 223, 70 (1949).

²⁴ Barmanton and Domow, Ben. 73, 44 (1940); Domow, Ben. 73, 155 (1940).

¹⁶ King and Work, J. Chem. Soc., 1397 (1949).

²² Eistern, Angew. Chem., \$4, 124 (1941).

Since the product obtained in the Anndt-Eistert synthesis is an acid, or a derivative which can be hydrolyzed to an acid, it is possible to continue the chain-lengthening process. The method is particularly adapted for the preparation of a homologous series of acids. In a number of casers two methylene groups have been added to the chain of an acid by carrying out two successive Arndt-Eistert syntheses. 11 Two methylene groups have been introduced into dicarboxylic acids in one operation (bishomologiation) by the Arndt-Eistert method. Thus, adipic acid has been converted to suberic acid, and sebacic acid to decane-1, 10-dicarboxylic acid through the intermediate historyketones. 11 ""

Little work has been done on the use of diazo compounds other than diazomethane in the Arndt-Eistert synthesis. It has been reported that the diazoketone obtained from p-nitrobarroyl chloride and diazoethane yielded p-nitrophenylmethylacetanilide when rearranged in aniline. 18

$$p$$
-NO₄C₄H₄COC1 $\stackrel{CH_2CHN_1}{\longrightarrow} p$ -NO₄C₄H₄CO $\stackrel{C}{\longrightarrow}$ C(CH₄)N₁
 p -NO₄C₄H₄CO $\stackrel{C}{\longrightarrow}$ C(CH₃)N₁ + C₄H₄NH₁ \rightarrow p -NO₄C₄H₄CH(CH₃)CONHC₄H₁ + N₁

Several earboalkoxydiaroketones, RCO—CN₂CO,R', formed by interaction of acid chlorides and diazoacetic ester, bave been submitted to rearrangement.¹ The diazoketone prepared from c-luroyi bromide and methyl diazoacetate yielded dimethyl c-luryfmalonate when rearranged in methanol in the presence of platinum.²

The chlorides of two hindered acids have been found to resist the action of diazomethane; these are the chloride of the acid ester of homocam-

- M Bachmann and Edgerton, J. Am. Chem. Soc., 62, 2550 (1940).
- 17 Bachmann and Holmes, J. Am. Chem. Soc., 62, 2750 (1940).
- Walker, J. Chem. Soc., 1304 (1940).
 Work, J. Chem. Soc., 1315 (1940).
- Work, J. Chem. Soc., 1315 (1940).
 Eistert, unpublished results. See ref. 25.
- ¹¹ Standinger and Maching, Ber., 49, 1973 (1916); Standinger, Becker, and Hirrel Ber., 49, 1973 (1916).
 - 49, 19.8 (1916).
 Reichstein and Morsman, Helv. Chim. Acta, 17, 1119 (1934).

phoric acid in which the acid chloride group is attached to a tertiary carbon atom 33 and mesitoyl chloride. 18

Unlike the acid chlorides of carboxylic acids, sulfonyl chlorides fail to react with diazomethane.34

Functional groups as phenolic hydroxyl, aldehyde, active methylene, and α,β-unsaturated carbonyl groups, which are capable of reacting with diazomethane, might be expected to interfere in the Arndt-Eistert synthesis. Only a few acid chlorides containing such groups have been studied. From 4-fluorenonecarboxylic acid chloride, the methyl ester of 4-fluorenoneacetic acid was obtained in 84% yield, 35 although the parent ketone, fluorenone, reacts with diazomethane. 36 Likewise, 2-hydroxy-3-naphthoyl chloride yields the diazoketone without methylation of the hydroxyl group. 37 However, it is not certain that the acid chloride group in other compounds containing reactive groups will react preferentially with the diazomethane.

One of the side reactions that occurs in the preparation of the diazoketones is the formation of ω -halomethyl ketones. As has already been pointed out, this reaction is not significant if the reaction is carried out at low temperature in the presence of an excess of diazomethane. If the diazoketone is treated with halogen acids, the ω -halomethyl ketone can be obtained in excellent yield, and this reaction has been used recently for preparative purposes.^{24c, 25, 23, 23}

Other side reactions apparently accompany the formation of some diazoketones, since the latter are sometimes contaminated with impurities as yet unidentified. In view of the reaction between acid chlorides and diazoacetic ester,^{21, 22} there is a possibility that the diazoketone formed

²² Litvan and Robinson, J. Chem. Soc., 1997 (1938).

²⁴ Arndt and Scholz, Ber., 66, 1012 (1933).

²⁵ Bachmann and Sheehan, J. Am. Chem. Soc., 62, 2687 (1940).

Schultz, Schultz, and Cochran, J. Am. Chem. Soc., 62, 2902 (1940).
 Krzikalla and Eistert, J. prakt. Chem., 143, 50 (1935).

²³ Haberland, Ber., 72, 1215 (1939).

initially may react with a second molecule of the acid chloride, but this has not been established.

EXPERIMENTAL CONDITIONS AND PROCEDURES

The acid chloride used in the first step of the Arndt-Eistert reaction may be prepared by any of the usual methods, but it should be carefully purified, by distillation whenever possible. The solvents and apparatus must be scrupulously dry, especially when aliphatic chlorides are employed, in order to avoid hydrolysis. Any free acid formed by hydrolysis will be converted to the methyl ester by the diazomethane, thus contaminating the product and decreasing the yield.

Diazomethane must be prepared with care. It is extremely toxic, and repeated exposure to even very low concentrations causes increased sensitivity to the substance. An account of a case of acute diazomethane poisoning has been published. A good hood with a forced draft is strongly recommended for work with diazomethane. Diazomethane is explosive in the gaseous state, and, although the ethereal solutions, which are generally used, are safe to handle at room temperature or lower, a certain amount of care must be exercised. Fortunately, an other solution of diazomethane can be prepared at 0° from N-nitrosomethylurea, and and the solution can be used without purification by distillation. An inexpensive method for preparing N-nitrosomethylurea from urea and methylamine hydrochloride has been described. Be should be mentioned that N-nitrosomethylurea has been known to explode when kept at room temperature, but when stored in a cold place the compound remains unchanged for months.

The preparation of diazomethane from N-nitrosomethylurethan ¹⁰ by von Pechmann's method is convenient for small amounts, although the diazomethane usually requires purification by distillation. The method consists in decomposing the urethan by means of a sodium alcoholate. Higher alcohols, such as propanol ¹⁰ and ethylene glycol, ⁴⁰ have been used to make the alcoholate in order to minimize contamination of the diazomethane.

Diazomethane has been prepared also from hydrazine, chloroform, and potassium hydroxide. A new method which appears attractive, but

^{**} Sunderman, Connor, and Fields, Am. J. Med. Scs., 195, 469 (1938).
** Arndt, Org. Syntheses, 15, 4 (1935).

⁻ Arnat, Org. Syntheset, 19, 4 (1935).

- Arnat, Org. Syntheset, 19, 4 (1935).

- Odenwald, Ann., 415, 223 (1915), 418, 317 (1919).

Werner, J. Chem. Soc., 115, 1006 (1919).

⁴ Arndt, Loewe, and Avan, Ber., 73, 606 (1940).

Hartman and Phillips, Org. Syntheses, 13, 84 (1933).
 Meerwein and Burneleit, Ber., 61, 1845 (1928).

[&]quot;Meerwein and Burneleit, Ber., 81, 1845 (1914).
"Staudinger and Kupfer, Ber., 45, 501 (1912).

which has not yet found extensive use, consists in the treatment of nitrosomethylaminomesityl oxide with sodium isopropoxide. The requisite intermediate is obtained readily from mesityl oxide, methylamine, and nitrous acid.

The concentration of diazomethane in a solution is estimated best by titration with benzoic acid according to the procedure of Marshall and Acree.⁴⁷

From a consideration of the reactions which occur on interaction of an acid chloride and diazomethane, it is evident that the acid chloride should be added to an excess of diazomethane, for in this manner the side reaction leading to the formation of the \(\pi\)-halomethyl ketone is suppressed. A solution (or suspension) of the acid chloride (1 mole) in ether or benzene is added slowly to a cold (0-5°) solution of diazomethane (3 moles) in ether or benzene with swirling or mechanical stirring of the mixture. Generally a brisk evolution of nitrogen takes place. With reactive acid chlorides, such as most aliphatic acid chlorides, the reaction appears to be complete as soon as addition has been made, but usually the mixture is allowed to stand at 20-25° for an hour or two. With aromatic and other less reactive acid chlorides, two hours and more (sometimes twelve to twenty-four hours) is generally allowed.

Some diazoketones crystallize from the solution as they are formed, or when the solution is cooled to -10° or lower. Usually they are isolated by evaporating the solvent under reduced pressure from a water bath held at 20-30°. As a rule, the residual diazoketone is satisfactory for rearrangement without further purification. If it is crystalline, the diazoketone may be purified by trituration with a small volume of cold solvent in order to dissolve oily impurities, and many diazoketones have been recrystallized. Purification by distillation is not recommended. Diazoacetone explodes when distilled at atmospheric pressure (113-115°), but it has been distilled without decomposition under reduced pressure. While most diazoketones appear to be stable under ordinary conditions, and some even in cold methanolic potassium hydroxide solution, the crystalline diazoketone obtained from cinnamoyl chloride and diazomethane is unstable and decomposes on standing.

For the rearrangement of the diazoketones to yield acids, esters, amides, and substituted amides, silver oxide is frequently employed. Freshly prepared silver oxide and commercial silver oxide have been used with equal success. The silver oxide may be prepared by adding a dilute solution of sodium hydroxide to a solution of silver nitrate (10%)

⁴⁶ Adamson and Kenner, J. Chem. Soc., 286 (1935).

⁶ Marshall and Acree, Ber., 43, 2323 (1910).

⁴⁸ Reichstein and v. Euw, Helt. Chim. Acta, 22, 1209 (1939); 23, 136 (1940).

until precipitation is just complete, nn excess of alkali being avoided. The silver oxide is washed several times with distilled water by decantation and then filtered by suction and washed well with water.

In order to prepare an acid, a diovane solution of the diazoketone is added slowly to a warm (60-70°) aqueous solution of silver nitrate and sodium thiosulfate or to a suspension of silver orde in a dilute solution of sodium thiosulfate. If the conversion the acid fails to give good results, it may be advisable to employ the procedures for making the ester or amide, which are obtained generally in higher yields than the acids, and obtain the free acid by hydrolysis of the derivative.

Esters of the homologous acids are prepared by adding silver oxide to a hot solution or suspension of the diazoketone in an anhydrous alcohol. Methanol, ethanol, and propanol have been used, methanol most frequently. The silver oxide is added generally in the form of a slurry in the alcohol, best results being obtained if it is added in portions over a period of an hour or two rather than in one lot. The silver oxide is reduced by hot methanol to metallic silver, which usually deposits as a mirror on the sides of the flast.

There is an appreciable difference in the rates with which various diazoketones rearronge and form esters. Sometimes the reaction is ecomplete in an hour; honever, as much as twelve hours may be necessary for completion of the reaction. The presence of unreacted diazoketone may be detected by the evolution of nitrogen which takes place when a sample of the solution is treated with a drop or two of concentrated hydrochloric acid. If if the reaction is slow, it may be advisable to continue the addition of more silver ovide. In a few resistant cases, the solution was filtered from the sludge of silver and silver ovide and the filtrate was treated with fresh silver coulde. In one preparation, it best results were obtained by refluxing a suspension of silver ovide in methanol until a thin silver mirror was formed (about fifteen minutes), then adding the diazoketone and continuing the refluxing.

The conversion of a diazoketone to an acid amide has been accomplished by passing ammonia into a cold solution of the diazoketone in ethanol containing a small amount of silver coide. The procedure has been reversed also and the diazoketone added to an ethanolic solution of ammonia, followed by the addition of silver oxide or silver nitrate. A more widely used scheme consists in treating a warm solution of the diazoketone in dioxane with a 10-25% aqueous solution of ammonia containing a small amount of silver nitrate, after which the mixture is heated for some time. *1" It would appear desirable to take precautions

⁴ Arndt and Elstert, Ber., 69, 1805 (1936).

(use of shield) when heating mixtures containing ammoniacal silver nitrate.

A number of procedures have been employed to prepare anilides from the diazoketones. Some have been prepared by the gradual addition of the diazoketone to boiling aniline; 1-27 after each addition one waits until the evolution of nitrogen has ceased before making another addition. A better procedure consists in warming a solution of the diazoketone and aniline in ethanol or dioxane containing a small amount of aqueous silver nitrate.⁵

Occasionally the product obtained in a reaction may contain traces of colloidal silver or silver salts. These may be removed by filtering a solution of the compound through alumina, after first making the solution alkaline if an acid is the product.

Preparation of Diazomethane

From N-Nitrosomethylurea. A mixture of 150 ec. of ordinary ether and 45 ce. of 40% aqueous potassium hydroxide is eooled to 5°. To this is added, with continuous eooling and efficient stirring or swirling, 15 g. of finely powdered N-nitrosomethylurea in small portions as rapidly as the crystals dissolve (a few minutes). The deep yellow ethereal solution of diazomethane can be separated from the aqueous layer by decantation or by means of a separatory funnel. The solution, which contains about 4.2 g. of diazomethane, is dried for several hours over pellets of pure potassium hydroxide or over soda-lime. A solution of diazomethane in benzene may be prepared in the same way. Larger runs may be made by varying the amounts of material accordingly.

From N-Nitrosomethylurethan.¹⁹ A solution of 2.8 g. of powdered potassium hydroxide (85%) in 10 cc. of warm propanol is prepared in a 125-cc. Claisen flask; 60 cc. of anhydrous ether is added to the solution, and the flask is attached to a dry condenser, which is connected to a receiver (a suction flask fitted with a drying tube) containing about 10 cc. of anhydrous ether. The end of the condenser dips below the surface of the ether in the receiver. Through a dropping funnel a solution of 4.5 cc. of nitrosomethylurethan in 10 cc. of anhydrous ether is dropped into the alkaline mixture; the diazomethane is distilled from the mixture as it is formed. The othereal solution contains between 0.72 and 0.9 g. of diazomethane and is suitable for reaction without drying.

Preparation of Acids

Conversion of α -Naphthoic Acid to α -Naphthylacetic Acid.^{2, 23} A solution of 19 g. of α -naphthoyl chloride in 50 cc. of absolute ether is added

at 5-10° to a solution of diazomethane prepared from 35 g. of nitrosomethylurca in 500 cc. of ether. After several hours at 20-25°, the ether is removed under reduced pressure, finally at 30°. The crystalline yellow residue of a-naphthoyldiazomethane (mp. of a sample after recrystallization from benzene, 54-55°) weighs 18 g. (92%).

A solution of 15 g. of the diazoketone in 100 cc. of dioxane is added dropwise with stirring to a mixture of 2 g. of silver oxide, 5 g. of anhydrous sodium carbonate, and 3 g. of sodium thiosulfate in 200 cc. of water at 50-60°. Stirring is continued for one hour after addition is complete, and the temperature of the mixture is raised finally to 90-100°. The solution is cooled, diluted with water, and acidified with dilute nitric acid. The α-naphthylacetic acid, which precipitates, is filtered from the mixture and recrystallized from water; yield, 10-12 g. (79-88%); m p. 130°.

Bishomologation. Sehacic Acld to Decane-1,10-dicarboxylic Acid (p. 45). An ethercal solution of schacyl chloride prepared from 20 g. of schacic acid is added slowly to an ethercal solution of diazomethane (prepared from 50 g. of nitrosomethylurca), and the mixture is allowed to stand overnight. The other and excess of diazomethane are removed under reduced pressure, and the residual crystalline 1,8-bisdiazoacetyloctane is collected; yield, 19.3 g (77%, based on the acid); m.p. 91°, after recrystallization from benzene.29

A solution of 6.8 g. of the diazoketone in 100 cc. of warm dioxane is added with stirring to a suspension of 7 g. of freshly precipitated silver oxide in 250 ec. of an aqueous solution containing 11 g of sodium thiosulfate at 75°. A brisk evolution of nitrogen occurs. After one and onehalf hours at 75°, the black silver residue is removed by filtration, the clear, almost colorless filtrate is acidified with nitric acid, and the decane-1,10-dicarboxylic acid is extracted with other. From the other extract, 4.5 g. (72%) of crude acid is obtained. After recrystallization from 20% aqueous acetic acid, it melts at 127-128°.18

Preparation of Amides

Conversion of p-Anisoyl Chloride to the Amide of p-Homoanisic Acid. To an ethereal solution of diazomethane obtained from 380 g, of nitrosomethylurea 150 g. of p-anisoyl chloride is added, and the solution is allowed to stand overnight. The solvent is removed by distillation, and the crystalline diazokctone is recrystallized from benzene, from which it separates as transparent, hexagonal prisms; m.p. 90-91°; yield, 109 g. (70.3%).

A solution of 20 g. of the diazoketone in 100 ee. of dioxane is treated with 150 ee. of aqueous ammonia (sp. gr. 0.9) and 30 ee. of 10% aqueous silver nitrate solution at 60-70°. The mixture is boiled under reflux for two hours, cooled, and the p-homoanisamide is precipitated by the addition of water. Recrystallization from ethanol yields 15 g. (81%) of the pure amide; m.p. 188-189°.

Preparation of Anthraquinone-2-acetanilide.⁸ To a solution of diazomethane in dioxane (prepared from 35 g. of nitrosomethylurea) is added 27 g. of anthraquinone-2-earboxylic acid chloride. When the reaction is complete, a few cubic centimeters of water are added and then 30 cc. of aniline and 30 cc. of 10% aqueous silver nitrate solution. A renewed evolution of gas occurs. The reaction is completed by heating on a steam bath. The product begins to separate while the mixture is still warm; after cooling, the product is filtered, dried, and recrystallized from xylene, from which the anilide is obtained as small, colorless needles; m.p. 267-268°.

Preparation of 2-Hydroxy-3-naphthylacetanilide.³⁷ To an ethereal solution of diazomethane prepared from 35 g. of nitrosomethylurea is added 25 g. of 2-acetoxy-3-naphthoyl chloride. After one-quarter hour at room temperature, the mixture is cooled for one hour at -15°, and the precipitated diazoketone [23 g. (90%); m.p. 122-123°, dec.] is filtered from the mixture.

Ten grams of the diazoketone is added in portions to 30 g. of boiling aniline; after each addition the reaction is allowed to run to completion before the next portion is added. The mixture is boiled for a short time after all the diazoketone has been added, cooled, and poured into dilute hydrochloric acid. The anilide is filtered from the mixture and recrystallized from ethanol or acetic acid; m.p. 215–216°; yield, 7.1 g. (58%).

Preparation of Esters

Preparation of the Ethyl Ester of α -Naphthylacetic Acid.^{25, 8} The diazoketone is prepared from the acid chloride of α -naphthoic acid in the manner described (p. 50). To a solution of 10 g. of the diazoketone in 150 cc. of ethanol at 55–60° is added a small amount of a slurry of silver oxide, prepared from 10 cc. of 10% aqueous silver nitrate and stirred with 30 cc. of ethanol. As soon as the evolution of nitrogen subsides, more of the silver oxide is introduced, and this process is continued until all the slurry has been added. The mixture is then refluxed for a short time, treated with charcoal, filtered, and evaporated. Distillation yields 8–9 g. (73–82%) of ethyl α -naphthylacetate, boiling at 175–178°/11 mm.

Preparation of the Dimethyl Ester of 7-Methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-8-propionic Acid 19 (p. 43). To 4 cc. of ice-cold dry benzene in a 125-cc, filter flask fitted with a drying tube are added 2 drops of pyridine and then 1.5 cc. of pure thionyl chloride. To the cold solution is added 1.71 g. of 7-methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (p. 43) in powdered form. After standing at room temperature for one-half hour, the mixture is warmed to about 40° for ten minutes. The orange-yellow solution, containing some pyridine hydrochloride in suspension, is evaporated under reduced pressure: 2 cc. of benzene is added, and the solution is evaporated again in order to remove traces of thionyl chloride. The crystalline acid chloride is dissolved in 16 cc. of warm benzene: the solution is cooled somewhat and decanted carefully (through a small plug of cotton in the side arm of the flask) drop by drop into a cold (5°) solution of diazomethane in other (prepared from 4.5 cc. of nitrosomethvlurethane); during the addition the diagomethane solution is saurled constantly.

After fifteen to thirty minutes, the other and excess of discomethane are removed under reduced pressure at room temperature. To the crystalling diazoketone is added 35 cc of aphydrous methanol, and to the warm (50°) mixture is added one-half of the silver oxide which has been prepared from 3.6 ec. of 10% aqueous silver nitrate solution and made into a slurry with methanol. The mixture is warmed on a water bath at about 60° with frequent swirling. Nitrogen is evolved, and after fifteen to twenty minutes all of the rather insoluble diszoketone has gone into solution. At this time a small amount of silver exide is added and the heating is continued; further additions of silver oxide are made every five minutes, so that after six additions all of it has been added. Then the mixture is refluxed for fifteen minutes, treated with Norit. filtered, and concentrated to a small volume. On cooling, the product crystallizes; vield, 1.48-1.56 g. (80-84%); m.p. 97-101°. If the crystals darken on exposure to light, a benzene solution of the product is passed through a short column of alumina io order to remove traces of silver compounds present.

SURVEY OF THE ARNOT-EISTERT SYNTHESIS

In the following table are given nearly all the examples of the synthesis which had been reported prior to November, 1941. The first column gives the name or formula, or both, of the acid used as the starting material. The acids are listed in the following order: aliphatic, cycloalkyl, arylalkyl, aromatic, and heterocyclic scids. Frequently an ester or amide of the homologous acid was prepared in the synthesis, and the derivative was then hydrolyzed to the free acid, the weight of which was recorded. The second column shows the product (acid, ester, or amide) which was prepared initially, and the third column indicates the compound which was isolated. The yields, which are reported in the fourth column, represent the conversion of the starting acid to the compound which was isolated and are the over-all yields for the three steps: preparation of the acid chloride, formation of the diazoketone, and rearrangement of the diazoketone.

PRODUCTS AND YIELDS OBTAINED IN THE ARMOT-EISTERT STATILESIS

Starting Acid	Primary Product	Compound Isolated	Yield, %	Yield, % Reference
Acetic acid	Amide	Proponsmide		- L
Ethyl hydrogen glutarate	Ester	Adipie neid	69	18
Adipie acid	Amide	Suberre acid	22.	88
Sebacic acid	Verd	Decane-I,10-drearboxylic acid	23	88
ביווילוו—לווכסיוו	Amide	Collection Circuit and Collection	8	83
oc dir.	Acid	oc cut	8	16
d-Pilopie acid	Yad	d-Homopalopic acid		:
	Amide	rac-Homotsopilopamide	1	162
2-Methylcyclohexenylacetic acid (p. 43)	And	raceEthyl homoisopulopate \$-(2-Methylcyclohexens1)-propionic acid	11	16a 17
6-(2-Methyleyeloliexenyl)-propionie acid	Ester Acid	Armide of the above acid Ethyl ester of the above acid 7-(2-Methylcyclobexeayt)-butyric acid	111	222
CII, C-CO, C.11,				
CIIQ-CII.	Verd	Hydrocamphorylacetic acid	53	g
CII, CII-CII,CO,II Ethyl hydrogen homocamphorate				

PRODUCTS AND YIELDS OPTAINED IN THE AUNDY-BISTRICT SYNTHESIS-Continued

ı	- 1	THE	AR	NDT-EISI	ERT S	YNTHESIS			
	Yield, % Reference	# 2 2 2	01	ij	53	23	2 2	25 25	25
	Yield, %	821	I	81	89	19	8 8	ខ្លួខខ្	
	Compound Isolated	7-Phenylbutyrio acid 7-Phenylbutyrio acid 6-Melhyt-7-phenylbutyrio acid	Annue of the thorse are graphed by h.p-Methylethylphenylpropionic acid	eta-Methyl-7-phenylvaleric acid	2-(1-Naphthyl)-valerie acid	7-(1-Phenanthryl)-butyria acid	7-(2-Phenanthryl)-valerie neid	γ-(.t-t neumnthryl)-vatering act. γ-(3-Phenanthryl)-vateramido β-(4-Methyl-1-phenanthryl)-propionic neid	y-(1-Mothyl-1-phemanthryl)-butyric acid
	Primary Product	Aeid Ester Aeid	Anndo Acid	Aeid	Bater	Ester	Ester	Amido Fister	Pster
LICODOCIS AND LIGHTS	Starting Aeid	CallaCltaCltaCOall p-Phenythreptionie neid CallaClta(Clta)Cl1COall	$_{ m cr}$ -Methyl- μ -phenylpropionie nerd ${ m G}_0\Pi_0({ m Cl}_1)({ m C}_2\Pi_0){ m CCO}_2\Pi$	Methylalhylphenylacotic acid C ₆ H ₆ (CH ₃)CH(CH ₃)CHCO ₂ H cc-Methyl-p-phenyllatyric acid CH ₅ CHCH ₂ CO ₂ H		β-(1-Naplathyt)-batyric neid CO ₂ 11 C1	CIII ₂ $\theta - (1 - Phomanthryb) - propionio acid$ $\theta - (2 - Phomanthryb) - butyric acid$	β-(3-Phenant hry1)-tuttyrio neut 4-Mot hyl-1-ahonantlurdacet ia acid	\$-(4-Mothyl-1-phemanthryl)-propionie neid

S	ક	22	58	28	20	59	8	3	1
	ę	8	87	g	12	88 27	1	ı	
7. C.	b-(r-acenapatuy)-propone acid	B-(1-Ethyl-7-acenaphthyl)-propionic acid	7-Methyl-7-(3-pyrenyl)-dutyrie acid	P.Methyl-y-(I-pyrenyl)-butyrie acid	a-Methyl ester of the homologous acid	B-Form of the above compound or-Methyl ester of the homologous acid	a-Methyl ester of the homologous acid	\$-Form of the above compound	
	Ester	Ester	Ester	Ester	Ester	Ester Ester	Ester	Ester	
Сиссон		7-Acenaphthylacetic acid 1-Ethyl-7-acenaphthylacette acid CH3	cit; co;u	6-Methyl-8-(3-pyrenyl)-propnonie acid a-Methyl-8-(3-pyrenyl)-propnonie acid CR ₁	Cu,coan	a-2-Methyl-2-arthomethoxy-1,2,3,4-tetrnhydro- pshitalenet-1-aette and \$-Torm of the above compound \$-2-Methyl-2-arthomethoxy-1,2,3,4,-tetrahydro- mathyl-1-a	a-6-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4- tetrabydronarhthalene-1-acete arid	β-Form of the above acid	* References 50-72 appear on p 52

Phoducts and Yerles Octained in the Anne-Besteut Synthesis-Continued

		中の一個の一個の一個の一個の一個の一個の一個の一個の一個の一個の一個の一個の一個の		de marielle bande stable emparente par
Sharling Acul	Primmry Product	Compound Isolated	Vield, 9, Ref	Yield, % Reference
CIL ³ COL ³ COL ³	Pketor	a-Methyl ester of the homologous acid	98	79
- 4-2-Methyl-2-eurhounethoxy-1,9,9,4-tetrabyelve-				
B-thrm of the above acid	Retor	Berm of the above compound	2	19
0-7-Methoxy-2-methyl-2-eurhomethoxy-(,2,3,4-	Bater	a-Methyl ester of the homelogous neid	2	2
to rehydrophennilinene-l-acetto acid	Paron	allown of the above community	80-81	Ξ
w-7-Nethoxy-2-ethyl-2-eurbomethoxy-1,2,3,4-tetra-	Ester	a-Methyl ester of the homelogous acid	£	2
hydrophount brone-1-acetic acid		11. min of the above manner	2	2
e-roun of the move from e-7-Mothoxy-2-n-propyl-2-earbonnethoxy-1,2,3,4-	Ester	a-Methyl ester of the homelogous acid	30-50	3 3
totrahydrophenanthrene-t-acetic neid	Pada	Commence of the city of the	83	68
p-point of the active acta	Pedor	Alabel actor of the homodown mit	2 5	3 2
tetrahydrophennulwene-t-neetle neid			3	8
B-Porm of the above acid	Bator	B-Porm of the above compound	;	33
v-7-Methoxy-2-mothyt-2-carbomethoxy-1,2,3,4-	Pister	w-Methyl ester of the homologous neid	ş	23
terims tree above acid	Pater	p-Porm of the above compound	Q.	8

a-9-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4-	Die	Ester . Methyl ester of the homologous acid	8	19	
P-Form of the above acid 9-Methoxy-2-cityl-2-carbomethoxy-1,2,3,4-tetra- iredon-invariance-acid	Ester	From of the above compound -Methyl reter of the homologius seid	F 2	2 3	
P. Form of the above acid P. Form of the acid acid acid acid acid acid acid acid	Die	Fform of the above compound e-Methyl ever of the homologous acid	Ŀξ	5 5	-
3-Form of the above acid	Fire	3-Torm of the above compound	=	19	
co,cui	Deter	e-Methyl eder of the bomologists acid	2	3	
OCII,	Ester	A-Form of the above compound	£	3	IIII
CH-O,	Acid	Directly1 ever of O-methyllomoretric arid	Poor	Ħ	
Monomethyl ester of 0-methylestric acid					

^{*} References 50-72 appear on p 62.

Synthesis-Continued	
Annor-Bistent	
THE	
Z	
ins Obtained in the Aundt-E	
Yields	
dNA	
Pronters AND YINIDS	

		THE ARNDT-EISTERT SYNTHESIS	
	Yield, % Reference *	66 8, 25 8, 25 8, 25 8, 25	
	Yield, %	69 41. 55 65 65 65 65 65 65 65 65 75 65 65 65 65 65 65 65 65 65 65 65 65 65	
	Compound Isolated	Ethyl ester of the homelogous acid Phenylacelamide Phenylacelamide a-Nitrophenylacetamide p-Nitrophenylacetamide aliazochane) a-Bromophenylacetic acid p-Homonisamide 3-1-Dimethaxyphenylacetic acid 3-1-Dimethylacetic acid Naphthylacetamide Ethyl e-maphthylacetato	Constitution of the contract o
NI GENIN	Primmy Product	Ester Amido Amido Amido Amido Ester Anido Amido Amido Amido Amido Amido Amido Amido Amido Anido Anido Anido	OF THE PARTY OF
PRODUCTS AND YIELDS OBTAINING IN THE	Starting Acid	CII ₃ COO Monomothyl ester of 3-acetoxyctiobilianio acid Boazoio ucid p-Nitrobenzoic acid p-Anieto acid p-Anieto acid 3,4-Dinathoxybenzoic acid 3,4-Crimathoxybenzoic acid 2-Biphenylexy-4-methoxybenzoic acid 2-Biphenylexy-4-methoxybenzoic acid 2-Liphenylexy-6-methoxybenzoic acid 2-Nitro-6-methyl-2-biphenylexrboxylio acid 2-Nitro-6-methyl-2-biphenylexrboxylio acid 2-Nitro-6-methyl-2-biphenylexrboxylio acid 2-Nitro-6-methyl-2-biphenylexrboxylio acid	

			T	ABL	E O	FPR	ODU	CTS	A A	ID	Υİ	EI	D	S					
13, 37	37			ž	3		22		67		00	60	o	20. 204	20	21	52	66	22
82-88	62			8	8		ä		83		ı	ı	1	28	1	33	20	l	24
Ester 2-Hydroxy-3-naphthylacetic acid	2-Hydroxy-3-naphthylacetanilide			A.Dinomenando and			Methyl 4-fluorenonescetate		1-Acenaphtbylacetic acid		Anthraquinone-2-acetanilide	1-Chloroanthraqumone-2-acetanilide	1-Nitroanthraquinone-2-acetaniide	Ethyl a-thienylacetate	Methyl a-thenylscetate	Thionaphthyl-3-acette and	Coumarone-3-acetie acid	Coumayone-3-acetamide	Ethyl coumarone-3-acetate
Ester	Anilide			Poler			Ester		Aeid		Andide	Anılıde	Andide	Ester	Ester	Yeld	Ester	Amide	Ester
H*00	OCCOCH1	2-Acetoxy-Snaphthoic acid	COM	Ç ENT	RAL	4-Fluoreneenrhoxylie acid	WAY	Coott		1-Acenaphthenecarboxylic acid	Anthraquinone-2-carbaxylic acid	I-Chloroanthragunone-Z-carboxylic acid	1-Nitroanthraquinone-2-carboxylic acid	a-Thiophenecarboxylic and (p. 44)		Intensport new 3-earboxy is acid (p. 44)	Counting the Section of the part (p. 44)		

- CENTRAL LIBRARY

* References 50-72 appear on p. 62

AND YIELDS ORTAINED IN THE ARNDT-EISTERT SYNTHESIS-Continued Ė

Products and Yields Officialist in the	rained in	THE THINKS		
Sharting Acid	Primary Product	Compound Isolated	Yield, %	Yield, % Reference
	Amido	Amido 4-Dibenzofurylacelamido	29	7.1
4.Dibenzofurancarboxylio acid 4.G-Dimethoxy-1-dibenzofurancarboxylio acid -Puroic acid	Amido Ester	4,6-Dimethoxy-1-dibenzofurylacelamide Dimethyl «furylmalonate (Using melhyl diazoacelate)	30	32
	Ester	Ethyl N-methylpyrrole-2-acelate	j	200
CH3 N-Methylpyrrole-2-carboxylio acid				
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71 Gilman, Parker, Bailie, and Brown, J. Am. Chem. Soc., 61, 63 Slotta and Müller, Z. physiol. Chem., 238, 16 (1936). ⁷⁰ Sehönberg and Warren, J. Chem. Soc., 1840 (1939). 69 Schöpf and Winterhalder, Ann., 544, 62 (1940). 2844 (1939).

⁷³ Gifman and Cheney, J. Am. Chem. Soc., **61**, 3149 (1939).

¹⁸ Buchmann and Carmack, J. Am. Chem. Soc., 63, 2494 (1941). 7 Baohmann and Sheehan, J. Am. Chem. Soc., 63, 2598 (1941). ¹⁵ Bachmann and Sheehan, J. Am. Chem. Soc., 63, 204 (1941).

59 Bachmann and Thomas, J. 11m. Chem. Soc., 63, 598 (1941). 60 Bachmann and Thomas, J. Am. Chem. Soc., 64, 94 (1942). o Bachmann and Wilds, J. Am. Chem. Soc., 62, 20St (1940).

CHAPTER 3

CHLOROMETHYLATION OF AROMATIC COMPOUNDS

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University of Illinois

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INTRODUCTION

The replacement of a hydrogen atom by a ehloromethyl group in a single operation has come to be known as ehloromethylation. The process may be illustrated by the earliest example, a synthesis of benzyl chloride earried out by Grassi and Maselli in 1898. These authors used benzene, hydrogen chloride, paraformaldehyde, and zinc chloride.

$$C_6H_6 + CH_2O + HCI \rightarrow C_6H_5CH_2CI + H_2O$$

Chloromethylation is of value in synthetic work inasmuch as the —CH₂Cl group can be converted to other groups such as —CH₂OH, —CH₀, CH₂CN, and —CH₃.

The present review has been limited to nuclear chloromethylation of aromatic compounds. Typical procedures are given, and an attempt has been made to indicate the scope and limitations of the reaction. The reactions are listed in tabular form.

THE SCOPE AND LIMITATIONS OF THE REACTION

Chloromethylation is generally applicable to aromatic hydrocarbons. Benzene, naphthalene, anthracene, phenanthrene, biphenyl, and many of their derivatives have been converted to chloromethyl derivatives. Terphenyl, however, resists chloromethylation altogether.² Monoalkyl benzene derivatives yield para chloromethyl compounds frequently accompanied by lesser amounts of the ortho isomers. A second chloromethyl group usually can be introduced, and sometimes excellent yields of dichloromethyl derivatives are obtained. Examples are the dichloromethyl derivatives of m-xylene ³ and mesitylene.⁴

$$\begin{array}{c} \operatorname{CH_2} & \operatorname{CH_2} & \operatorname{CH_2} & \operatorname{CH_2} \\ \\ \operatorname{CH_2} & \operatorname{CH_2} & \operatorname{CH_2} & \operatorname{CH_2} \\ \\ \operatorname{CH_2} & \operatorname{CH_2} & \operatorname{CH_2} & \operatorname{CH_2} \\ \\ \operatorname{CH_2} & \operatorname{CH_2} & \operatorname{CH_2} & \operatorname{CH_2} \\ \end{array}$$

The presence of a halogen atom on the ring causes the reaction to be more difficult to effect. Although such compounds as bromo- and chlorobenzene, bromo- and chlorotoluenes, and p-dichlorobenzene can be chloromethylated, the yields are frequently low. More highly halo-

¹ Grassi and Maselli, Gazz. chim. ital., 28, II, 477 (1898).

² v. Braun, Irmish, and Nelles, Ber., 66, 1471 (1933).

² v. Braun and Nelles, Ber., 67, 1094 (1934).

⁴ Nauta and Dienske, Rec. trav. chim., 55, 1000 (1936).

genated derivatives generally fail to undergo chloromethylation might be expected, however, halogen derivatives of polymethylbenzenes sometimes react readily to give high yields of chloromethyl compounds. Bromomesitylene is an example.

$$\begin{array}{c} \text{CH}_{2} \\ \text{CH}_{3} \\ \text{CH}_{4} \\ \text{CH}_{2} \\ \text{CH}_{2} \\ \text{CH}_{3} \\ \end{array} + \begin{array}{c} \text{CH}_{2} \\ \text{CH}_{3} \\ \text{CH}_{4} \\ \text{CH}_{5} \\ \text{CH}_{5} \\ \end{array} + \begin{array}{c} \text{CH}_{2} \\ \text{CH}_{5} \\ \text{CH}_{5} \\ \text{CH}_{5} \\ \text{CH}_{5} \\ \end{array}$$

Nitro groups tend to inhibit the reaction. Nitrobenzene, 6. 7 o-nitrotoluene, n-nitrotoluene, nitromesitylene, and 1-nitronanhthalene have been found to give chloromethyl derivatives, but usually in low yields. m-Dinitrobenzene and 1,3,5-trinitrobenzene, as well as o- and p-chloronitrobenzene, fail to react.

Ketones are generally unreactive. Acetophenone appears to react,7 but benzophenone and anthraquinone are recovered unchanged, However, chloromethylation is successful with ketones such as acetomesitylene, acetoisodurene, and 2.4.6-triethylacetophenone.

Phenols, as might be expected, react so readily that the reaction generally goes too far, yielding polymeric materials. The presence of a nitro group counteracts this tendency; satisfactory yields from nitrophenols have been reported, 3- 10- 11 A suitable device for getting around the difficulty with phenois is to convert them to esters by treatment with cthyl chlorocarbonate; the ethyl aryl carbonates can be chloromethylated successfully.17. 13. 14

The most important side reaction is that leading to the formation of the corresponding diarylmethane derivative. Highly reactive compounds of many sorts-naphthalene, anisole, phenols, polymethylbenzenes, etc.-tend to yield this type of product, and it is often difficult or impossible to isolate the intermediate chloromethyl derivative. Examples are α- and β-naphthol.15

- Fuson, Kneisley, Lindsey, Rabjohn, and Sperats, unpublished work.
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- 11 Ger pat., 132,475 (1900) [Chem Zentr. 73, II, 81 (1902)].
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- 12 Sommelet and Marszak, Compt. rend . 198, 2256 (1934).
- 4 Sommelet, Compt. rend . 197, 256 (1933).
- 16 Casturioni, Gozz, chim. stal., 67, 324 (1937).

Aromatic amines react very readily, but it has not been possible to isolate their simple chloromethyl derivatives. These could hardly be expected to be stable, since the highly reactive ehloromethyl group would undoubtedly condense with any amino group that might be present in the molecule.

In a study of the effect of substituents on the ease of chloromethylation of benzene by chloromethyl ether in the absence of a catalyst, Vavon, Bolle, and Calin have found that the rate is increased by —CH₃, —C₂H₅, —C₃H₇, —OCH₃, and —OC₂H₇, and diminished by —Cl, —Br, —I, —CH₂Cl, —CO₂H, and —NO₂. These effects are illustrated by the following relative rates of reaction.

Benzene	1
Toluene	3
m-Xylene	24
Mesitylene	600
Anisole	1,300
3,5-Dimethylanisole	100,000
Chloromesitylene	2
Nitrobenzene	Too slow to measure
Nitromesitylene	Too slow to measure

PROCEDURES

The procedure for chloromethylation has been modified in numerous ways. The formaldehyde may be added as formalin, or it may be generated in the reaction mixture by depolymerization of paraformaldehyde (trioxymethylene). (The terms paraformaldehyde and trioxymethylene, used interchangeably in the literature, refer to the polyoxymethylenes—polymers having the structure HOCH₂O(CH₂O)_nCH₂OH. The trimer (CH₂O)₃, melting at 62–63°, is called alpha-trioxymethylene.¹⁷ It is anhydrous, whereas paraformaldehyde generally contains from 2 to 5% of water.) Instead of formaldehyde and hydrochloric acid, diethyl or dimethyl formal and hydrochlorie acid may be used. When chloromethyl ethers or dichloromethyl ether are employed, the reaction usually can be effected without hydrochloric acid.

Catalysts may or may not be required. Among the catalysts which have been found to be especially useful are zinc chloride, sulfuric acid, and acetic acid. Yields with *p*-bromotoluenc are increased about three-fold by mixing a little aluminum chloride with the fused zinc chloride.¹⁵

¹⁶ Wagner, J. Am. Chem. Soc., 55, 724 (1933).

¹⁷ Pratesi, Gazz. chim. ital., 14, 139 (1884).

¹⁸ Fieser and Seligman, J. Am. Chem. Soc., 57, 942 (1935).

Blane "introduced the —CH_CI group into aromatic hydrocarbons by means of a mixture of formalin or paraformaldehyde and hydrochloric acid in the presence of zinc chloride. Darzens and Lévy, "in their syntheses of derivatives of naphthalene, employed paraformaldehyde and hydrochloric acid in acetic acid solution. Quelet and his co-workers, "": who have carried out numerous syntheses starting with aryl ethers, employed formalin and hydrochloric acid, with or without a catalyst, and modified the technique according to the sensitiveness of the chloromethylation product which was expected. Varon, Bolle, and Calin," as has already been stated, developed a technique permitting them to follow the course of the reaction and to study the influence of substituents on the case of introduction of the —CH_CI group. They used chloromethyle ther, without a catalyst, usually in acetic acid solution.

The most successful method for the chloromethylation of aromatic hydrocarbons is that of Blanc. 19 It has been modified in various ways. The preparation of benzyl chloride illustrates one of these variations.

Chloromethylation of Benzene 19 (Method of Blanc)

A mixture of 600 g. (7.7 moles) of benzene, 60 g. (2 moles) of paraformaldehyde,* and 60 g. of pulverized zinc chloride f is heated to 60° with stirring. While this temperature is maintained, a rapid stream of hydrogen chloride is passed into the reaction mixture until no more gas is absorbed dabout twenty minutes). The organic layer is removed,

- It is possible to use 40% formain in place of poraformaldehyde. In this case more sine chloride is required. The following proportions are most satisfactory 400 g, of beaten, 75 g, of 40% formain, and 100 g of pulserized sine chloride. The reaction is carried out as described, if allowed to run twelve hours, a 70% graded of diphenylmethane is obtained.
- † If the proportion of sinc chloride is increased, the yield of dichloromethyl derivative is correspondingly greater; if less sinc chloride is used, almost up dichloromethyl compound is produced but the yield of benuty chloride is diminished.
 - 19 Blane, Bull. soc. chim., [4] 33, 313 (1923).
 - 10 Darrens and Lévy, Compt. rend., 202, 73 (1936).
 - Quelet, Compt. rend., 198, 102 (1934).
 Quelet and Anglade, Bull, soc. chim., [5]3, 2200 (1936).
 - ¹¹ Quelet and Angisde, Bull. soc. chim., [5] 5, 220 (1930).
 ¹¹ Quelet and Allard, Bull. soc. chim., [5] 6, 620 (1937).
 - 11 Quelet, Bull. soc. chim , [4] 53, 510 (1933).
 - 25 Quelet, Compt. rend., 196, 1411 (1933). 26 Quelet, Bull. soc. chim. [5] 1, 539 (1934).
 - Quelet, Bull. soc. chim., [5] 1, 539 (1934).
 Quelet, Bull. soc. chim., [5] 1, 904 (1934).
 - 14 Quelet and Allard, Compt. rend , 205, 238 (1937).

washed with water and then with dilute sodium bicarbonate,* dried over calcium chloride, and fractionally distilled. After the excess benzene has been removed there is obtained 200 g. (79%) of benzyl chloride; b.p. 70° (15 mm.).

There are also produced about 12 g. of p-xylylene dichloride, m.p. 100° , and a small amount of diphenylmethane.

Although the reaction usually is earried out with zinc chloride as the catalyst, sulfuric acid and aluminum chloride have been used also. These catalysts are sometimes objectionable because they tend to favor the formation of diphenylmethane derivatives. For the chloromethylation of compounds which do not react readily, stannic chloride has sometimes been found to be a superior catalyst. The use of stannic chloride as the catalyst is exemplified by the preparation of 2,4,6-triisopropylbenzyl chloride. This method is interesting also because chloromethyl ether is used in place of formaldehyde or paraformaldehyde.

Chloromethylation of 1,3,5-Triisopropylbenzene 5

$$(CH_3)_2CH \xrightarrow{CH(CH_3)_2} + CH_3OCH_2Cl \xrightarrow{SnCl_4}$$

$$CH(CH_3)_2 \xrightarrow{CH(CH_3)_2}$$

$$(CH_3)_2CH \xrightarrow{CH(CH_3)_2}$$

$$CH(CH_3)_2$$

Three hundred grams of paraformaldehyde and 400 cc. of methanol are mixed and cooled. A rapid stream of hydrogen chloride is passed through the mass until two layers form and all the paraformaldehyde has disappeared. It is necessary to keep the mixture cool to prevent the formation of methylal. About 300–400 g. of hydrogen chloride is required. The upper layer is separated, dried over calcium chloride, and fractionated several times. The product boils at 57–59° and is about 90% pure. By washing with concentrated hydrochloric acid, it is possible to obtain a product which is 95% chloromethyl ether.

^{*} It is absolutely necessary to remove all the zinc salt by the washings. Without this precaution the product almost completely resinifies during the distillation period.

Sommelet, Compt. rend., 157, 1443 (1913).
 Reyschuler, Bull. soc. chim., [4] 1, 1195 (1907).

A mixture of 300 g. (1.47 moles) of 1.3.5-triisopropylbenzene* and 200 g. (2.5 moles) of chloromethyl ether is diluted with 600 cc. of carbon disulfide and cooled to 0°. To this solution is added, over a period of one hour, 120 g. (0.46 mole) of stannie chloride. The reaction mixture is stirred during the addition and for one hour afterward. It is poured on ice, and the organic layer is separated and dried over calcium chloride. Removal of the solvent and distillation of the residue in vacuum gives the benzyl chloride in yields of 300-315 g. (81-85%); b.p. 129-130° (4 mm.).

The chloromethylation of highly alkylated benzenes generally can be accomplished without any catalyst. It is sufficient to treat the hydrocarbon with a mixture of formaldehyde and concentrated hydrochloric acid.44 The chloromethylation of n-xylene, for example, is conducted in the following manner.

One mole of the hydrocarbon is mixed with an equal weight of 37% formalin (1.3 moles of formaldehyde) and five times its weight of concentrated hydrochloric acid. The mixture is stirred at 60-70° for seven hours, during which time a stream of hydrogen chloride is introduced. The resulting oil is taken up in other, and the solution is dried. Distillation gives 106 g of a fraction which is chiefly 2,5-dimethylbenzyl chloride (I); b p. 103° (12 mm.). A second fraction, amounting to about 10 g... consists mainly of a 'a dichlorodurene (II); m p. 133°. A very small amount of a 2 a 3-dichloroprehnitene (III) (m.p. 68-70°) also can be isolated

The chloromethylation of naphthalene has received much attention. Although, by the use of petroleum ether in the Blanc method, the reac-

^{*} The Dow Chemical Company product. Alkazens-13, was used.

tion gives yields of 30% of the theoretical amount,¹² other methods have been found to be more useful. Darzens and Lévy ²⁹ and, more recently, Ruggli and Burckhardt,³¹ Jones,²² Fieser and Novello,²³ Fieser and Gates,³⁴ and Cambron ³² have obtained the chloromethyl derivative by using a large amount of glacial acetic acid as a solvent for the hydrocarbon. Cole and Dodds ²⁵ preferred to carry out the reaction in an aqueous mixture with sulfuric acid as the catalyst.

The procedure of Cambron is as follows.

Chloromethylation of Naphthalene 25

A mixture of 288 g. (2.25 moles) of the hydrocarbon, 90 g. (3 moles) of paraformaldehyde, 250 g. of glacial acetic acid, 280 cc. of concentrated hydrochloric acid, and 135 cc. of syrupy phosphoric acid is heated, with efficient stirring, at 98–100° for four and one-half hours. The reaction mixture is then poured into 2 l. of cold water. The aqueous layer is decanted from the heavy oily layer, which is washed two or three times with 2-l. portions of water. After each washing the water is removed by decantation. The oil is filtered to remove the small amount of solid material and distilled under reduced pressure. The yield of α -chloromethylnaphthalene is 223 g.; b.p. 145–160° (6–8 mm.). This is 56.5% of the theoretical yield based on the amount of naphthalene used.

Phenols and their ethers, as has been indicated, react much more readily than the hydrocarbons. For anisole and the methyl cresyl ethers, monochloromethylation with 35-40% formalin and hydrochloric acid is most successful if conducted at 0-15° and without a catalyst. Higher temperatures and the presence of zinc chloride favor the formation of diphenylmethane derivatives and also dichloromethylation products. Phenyl esters, hydroxy aldehydes, ethers of hydroxy aldehydes, nitrophenols, nitrophenyl ethers, and highly alkylated ketones generally require mild conditions also.

An interesting illustration is the synthesis of 2-hydroxy-5-nitrobenzyl chloride by chloromethylation of p-nitrophenol. Methylal is used as the source of formaldehyde, and a little sulfuric acid is added to accelerate the reaction.

²¹ Ruggli and Burckhardt, Helv. Chim. Acta, 23, 441 (1940).

Jones, U. S. pat., 2,212,099 [C. A., 35, 462 (1941)].
 Fieser and Novello, J. Am. Chem. Soc., 62, 1855 (1940).

²⁴ Fieser and Gates, J. Am. Chem. Soc., 52, 2335 (1940).

²⁵ Cambron, Can. J. Research, 17B, 10 (1939).

²⁵ Coles and Dodds, J. Am. Chem. Soc., 60, 853 (1938).

Chloromethylation of à-Nitrophenol 15

A mixture of 50 g. (0.36 mole) of p-nitrophenol, 650 cc. of concentrated hydrochloric acid, 5 cc. of concentrated sulfurin acid, and 75 g. (1 mole) of methylal is stirred for four to five hours at 70-72°. During this period hydrogen chloride is passed into the reaction mixture. About an hour after the reaction is begun the 2-hydroxy-5-nitrobenryl chloride begins to separate. It is removed by filtration after the reaction mixture has been chilled. The vield is 46 g (69%).

Ketones having mesityl, duryl, isoduryl, or other highly alkylated aryl radicals undergo chloromethylation in yields of 25 to 88%. The procedure employs paraformalelyhde and concentrated hydrochlorou acid, but no catalyst. The chloromethylation of acotomesitylene gives very satisfactor results.

Chloromethylation of Acetomesitylene

$$\begin{array}{c} \text{COCH}_1 \\ \text{CH}_2 \\ \text{CH}_3 \\ \text{CH}_4 \end{array} + \begin{array}{c} \text{CH}_1 \\ \text{CH}_2 \\ \text{CH}_3 \\ \text{CH}_5 \end{array} + \begin{array}{c} \text{COCH}_5 \\ \text{CH}_5 \\ \text{CH}_5 \end{array}$$

A mixture of 40 g. (0.25 mole) of acetomesitylene, 9 g. (0.3 mole) of paraformaldehyde, and 150 cc. of coacentrated hydrochlora caid is shaken on a mechanical shaker overnight at room temperature. The at-chloracetoisodurene precipitates from the reaction mixture in clusters of almost white needles. These are removed by filtration and washed with water. They are recrystallized from low-boiling petroleum ether, then from methanol. There is obtained 40 g. (77%) of pure material; m.p. 74.5-75.5°.

RELATED REACTIONS

The expectation that condensations analogous to chloromethylation would take place if other aldehydes or other halogen acids were employed has been realized in a number of instances.

Bromomethylation. By the use of hydrogen bromide in place of hydrogen chloride it has been possible to prepare bromomethyl derivatives. The archives are all an entirely and a 1, a 4-dibromo-p-xylene 6 have been made in this way. Ethyl anisate, salicylaldehyde, salicylic acid, sand phenyl ether also undergo bromomethylation. Darzens that the method is general but that the yields are lower than in chloromethylation.

Iodomethylation. Iodomethylation has been reported by Sandin and Fieser ⁴² who converted 9-methyl-1,2-benzanthracene (I) to 9,10-dimethyl-1,2-benzanthracene (III) through the intermediate iodomethyl derivative (II). The iodomethylation was carried out by treating the bydrocarbon with chloromethyl ether or paraformaldehyde in glacial

$$\begin{array}{c|c} CH_3 & CH_3 & CH_3 \\ \hline \\ CH_2I & CH_3 \\ \hline \\ II & III \\ \hline \end{array}$$

acetic acid solution and then adding hydriodic acid (sp. gr. 1.7). The bright yellow iodomethyl compound formed in yields of 90%.

This preparation is especially interesting in the light of the failure of Badger and Cook to isolate the corresponding chloromethylation product. 43

Chloroethylation. By the use of paraldehyde in place of formaldehyde it has been possible to effect chloroethylation. Anisole and its homologs, when treated with paraldehyde and hydrochloric acid, give the corre-

³⁷ Tschunkur and Eichler, Ger. pat., 509,149 [C. A., 25, 711 (1931); Chem. Zentr., 102, I, 360 (1931)].

³⁸ Ger. pat., 114,194 (1900) [Chem. Zentr., 71, II, 928 (1900)].

³⁹ F. Bayer and Company, Ger. pat., 113,723 (1900).

⁴⁰ Brunner, Ger. pat., 569,570 [Chem. Zentr., II, 609 (1933)].

⁴¹ Darzens, Compt. rend., 208, 818 (1939).

⁴² Sandin and Fieser, J. Am. Chem. Soc., 62, 3098 (1940).

⁴³ Badger and Cook, J. Chem. Soc., 802 (1939).

sponding chloroethyl derivatives in yields of 40-60%. 27, 44, 45, 48, 47 synthesis of 4-methoxy-a-chloroethylbenzene is an example.

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ &$$

Xylene also has been chloroethylated.45 The chloroethyl derivatives readily lose hydrogen chloride, yielding the corresponding vinyl derivatives. Anisole gives a 90% yield of p-vinylanisole accompanied by a 10% yield of the artha isomer.44

Chloroacetaldehyde can be used also; with anisole it gives a.8-dichloroethylanisole.43

Chloropropylation. Chloropropylation of anisole followed by dehydrochlorination furnishes a synthesis of anethole.40

Chlorobutylation. Chlorobutylation of anisole has also been reported. 45, 45, 49 By using butyraldehyde, Ducasse 49 obtained 2-methoxy-5-methyl-α-chlorobutylbenzene in a yield of 30%. Chloroisobutylation of anisole has likewise been effected.45

⁴⁴ Quelet, Compt. rend., 199, 150 (1934). 4 Sommelet and Marszak, Fr. pet., 787,655 [C. A., 30, 1185 (1936)].

⁴⁴ Quelet, Bull, soc. chim., [5] 7, 195 (1940).

¹⁷ Quelet, Bull, soc. chim., [5] 7, 205 (1940). 49 Quelet and Allard, Bull, soc. cham., [5] 7, 215 (1949).

[&]quot; Ducasse, Bull. soc. chim., [5] 3, 2202 (1936).

TABLES OF DATA ON CHLOROMETHYLATION

The following tables list compounds which have been chloromethylated, together with the reaction products. References have been given to pertinent literature sources. Where available, the per cent yield is indicated in parentheses following the reference number.

The compounds have been arranged, according to the nature of the parent substances, in five groups: hydrocarbons (Table I), halogen and nitro derivatives of hydrocarbons (Table II), phenols and phenyl esters (Table III), ethers and thioethers (Table IV), and aldehydes and ketones (Table V).

TABLE I
CHLOBOMETHTLATION OF HYDROCARBONS

Attendences 50-60 appear on p 90,
Figures in parenthoses indicate the per cent yields

	1).
TABLE I-Continued	Chromomity Lation of Ityphogambons—Continued

51 633 FT 614 633 FT 614 633		References, and Yields † Mesitylene 4, 7, 29, 50(85), 53 Mesitylene 1(77) Durene 5(70) Frednitene	Product Olls	CHLOROMETHYLATION OF AROMATIC COMPOUNDS
Pseudoenmene 7, 37, 50(60), 52, 55(70)	CII,	t-		

* Heferences 50.40 appear on p. 90.

Product	(CII,),C—CII,CI	cur,	c,II.	(CII,),CII — CII,CII,),	C,Hu,———————————————————————————————————	
Parent Compound, References,* and Yields †	1,3-Dimethyl-5-t-butylbenzene 5		1,3,5-Tricthylbenzene 5(72)	1.3.5-Trisopropylbenzene 5(80), 56(94)	Cyclohexylbenzene 2(60)	Biphenyl 2(20), 7, 37, 50 Biphenyl 2(12),6
Product	(CII,),CII—CH,	Not isolated	car————————————————————————————————————	c,u,r	(CII.), C—(C.II.)	(CH ₁),C—(CH ₁)
Parent Compound, References, and Yields †	p-Cymene 19(76), 29, 37, 52	IsobutyI-p-cymene	n-Butylbenzene 62	t-Amylbensene 62	p-t-Butylethylbensene 57	p-Butyltoluene 52, 57

* Reference 50-90 appear on p 90.
† Figures in parentheres indicate the per cent yields.

TABLE I—Continued
Gheonomythyparion of Induced

*			
Parent Compound, References, * and Yields †	Product	Parent Compound, References, * and Yields †	Product
			CH1,
Bibonzyl 58	$\left[\text{CIII,C-}\left(\right)-\text{CIII,}\right]_{1}^{(7)}$	c-Methylnaphthalono 7, 20	
Hydrindone 50	CIII,o	β-Mothylnaphthaleno 20	CIT,CI
Nuphtlinlene 6, 7, 19(35), 20(95), 31(62), 32, 33(45), 31(63), 35(56), 37, 60a(42), 60, 61, 63	Olt, CI	Isononylnaphthalene 66(90)	CII,CI
	CIII'C	Diisopropylnaphthalene 56(86)	
Naphthalene 59a, 64, 65		Isododecylnaphthalene 56(92)	
	OII;OI	n-Dodecylnaphthalene 58(50)	
* References 60-00 morning on a 00			

* References 50-80 appear on p. 90.
† Figures in parentheses infleate the per cent yields.

net		CILICO	\subset	\supset	ch,cı			1
Product			\ \ 		CH Not isolated	Not isolated	Not isolated	
Parent Compound, References,* and Yields †	Phononelle	64, 70, 71		1,2-Benzanthracene 43(69), 68, 72,	9-Methyl-1,2-benzanthracene	3,4-Benzpyrene	20-Methylcholanthrene 43	
Product		8	CILC	φ	Not isolated CH ₂ Cl	£	CH-CI	
Parent Compound, References, and Yields	Tetralin 7(50), 66, 67, 68	Tetralin ‡ 7(9), 32		Tetralin 64, 60	Acenaphthene 64	Anthracene 6, 43, 64		• References 50-90 appear on p 90

" Retermine Model appear to p. pp. Theorem spaces where the desire the per cent packs I A 20% yield of behindmerkyletrillan has been reported by Armed and Barme, J. Am. Chem. Sta., 64, 2383 (1643).

Todomesitylene Not isolated Task(43) CHI, CHI, CHI, CHI, CHI, CHI, CHI, CHI,	Product Frent Compound,	Product
Not isolated CHI, CHI, CHI, CHI,	ACCEPTOCS, and Yield	
CHT CHT		`(-
CHI.	Cilic Cilic	CIII-
CH, CH,		CHI, CHI,
CH CH	<u>_</u> =	Br City
CH B	Circ	סוויסו
i i	2-Bromoethylbengene	((
THE CHI	Cit, Cit,	CILLO
734(36)	CII,CI	O HID
	\supset	Br C.H.
CH,	CH,	() CIII'CI (I)

* References 50-90 appear on p 90, f Figures in parenthests indicate the per cent yields,

TABLIS II-Continued

NH-Continued	Product	$CII_3 - CII_3CI$	CIII,—CIII,—NO,	CHI'sC Not isolated	-CZ
э Винуачичия об Иувносанво	Parent Compound, References,* and Yields †	o-Nitrotolnene	p-Wilrotoluene	Nitromesityleno 7	1-Nitronaphtlmlevo 76
Colonomication of Halogun and Newo Dunivatives of Hydrocandons—Continued	Product	CIII,—COII-CIICIII	CHII, C		NO ₂ —CII ₂ CI
Спгономили	Parent Compound,	l-Chlora-l-mesityhropono		a*-Chloroisodurono 7	Nitrahenzona 6, 7

* References 80-40 appear on p. 90.

§ Mures la parentheses hidloute the per cont yields.

TABLE III
CHLOROMETHYLATION OF PHENOLS AND ASST. FATTER

il Esters	unyound, and Yields † Product	сил.о	по-сп.	NO, CH.C	CHIC IIO
HENOLS AND ART	Parent Compound, References, and Yields !	p-Cresol	e-Nitrophenol 9, 11	m-Nitrophenol 79a(15)	p-Nitrophenol 10(69), 11
CHOROMETHYLATION OF PHENOLS AND ART. ESTERS	Product	Curo cur	HO CH,CH	CILL CILL	CIH,O
	Parent Compound, References, and Yields †	Phenol	o-Chlorophenol 9, 11, 61, 78	70(90)	o-Cresol

* References 50-90 appear on p. 90 † Figures in parentheses indicate the per cont yields

TABLE III—Continued

	CHLO	ROMET	HYLAT	ION OF	AROMA	TIC CON	IPOUNDS	
	Product	CIII,C—(CILIA	CIII,C-(-)-0C0,C;II,	0011,	CIIIIO	Cili, OCOCII,	
Сигономичить в Римови Амр Анть Витине-Сонтиней	Parent Compound, References, * and Yields }	Ruyl 3,5-xyfyl carbonate 12,13(60)		Rthyl thymyl earbonate 12, 14	P. P. L. Comments	13(60)	Diacetata of 2,6-Dimethyl-3- ethyllydroquinone 796(33)	
Chiohomethylation of Phinos	Product	CIII,C-()-0C0,CiII.	CIII,C-()-0C0,C1II,	CIII,C-(COO,C,III Rithyl thymyl enrhonnto	CIII,C—(CIII,	CII,-(-)-0C0,C,III,	CIII,——————————————————————————————————	
	Parent Compound, References, * and Yields †	Ethyl phenyl eurhonato 12(60), 14(60)	Ethyl o-chlorophonyl carbanate 14	Ethyl ceresyl carbonato	Ethyl <i>m</i> -cresyl carbonato 12, [3(30), 1-t	Piliyl p-cresyl antbounto t2, 14	Fkhyl 3,4-xylyl carbonate 12	

* References 60-90 appear on p. 90.

Parent Compound, References, and Yields †	Product	Parent Compound, References, and Yields †	Product
Dacetate of pseudocumo- bydroquinons 70c(73)	CH, OH CH,CI	Salicylic acid	OH CO.II
Dthyl ankate 7	Not isolated	m-Hydroxybensoio acid 39 P-Hydroxybensoic acid 39	OH CHACI
Anisyl acetato	Not included	6-Hydroxynaphthoic acid 39 m-Cresotinic acid 39	H 00

TABLE IV

Cheoromethyeation of Ethers and Thioethers

† Product	Ollia CII, OCII,	CII,0—(CII,CI	CH1,0—CH1,	CII,0—CII,CII		
Parent Compound, References, * and Yields †	Methyl p-cresyl ether 7, 21(75), 22(60), 81, 83(75), 85, 86, 86a(90)	Methyl 3,6-xylyl ether	Methyl 2,4-xylyl ether 7	Methyl thymyl ether 7, 21(70), 23	Phenetolo 13(70), 21, 45	
Product	CII,0—{\rightarrow}\rightarrow\circles	CIII,C	CII.O	cıı,o—()—cıı,cı	CII,0—CII,CI	
Parent Compound, References, * and Yields †	Anisole 6, 7, 13(60), 21(50), 22, 45, 70d(50), 80, 82(60), 83, 84	Anisole 79d(7), 84	Anisole 22(60), 79 <i>d</i> , 81, 82, 85, 86	Mothyl o-cresyl ether 21, 22(40), 83	Mothyl <i>m</i> -cresyl ether 7, 21, 83(26)	* Defendance 50.00 amages on a no

* References 50-90 appear on p. 90.

† Figures in parentheses indicate the per cent yields.

Parent Compound.		Parent Compained	
References, and Yields	Product	References," and Yields +	Product
n-Butyi phenyi ether 13, 45	c.n.o	Dimethyl ether of 2,6-dimethyl-	C,III, OCIII, CII
Methyl mesityl ether	CII, CII,CI	736(100)	cu, cu, cu,
	GII	Dimethyl ether of 2,6-dimethyl-	CIII, OCIII, CIII, CII
Hydroquinone dimethyl ether		3-ethylhydroquinone 796(100)	c,III, dolli,
81, 85, 80	CHILO-	3.6-Dimethoxypveudocumene	CHA-CH,
Dimethyl ether of 2,3-dimethyl-	CII, CII,CI		CII.
5-thylhydroquinone 70k(89)	CIII,	m-Chioroanisole 81, 85, 86	CH'O-CH'C
	0011		cm,c

* References 50-60 appear on p. 90 † Figures in parentheses indicate the per end yilds

PARILE IV-Continued

	40:11 E	Promes	Not isoluted	O-CII;CI	CIII.S.		CII.S—CII,
TABLE IV—Continued Continued Continued		Parent Compound, References, and Yields †	Anisio acid	7 Phenyl ether 40	Yothyl nhonyl thinether	81, 85, 86, 90	Methyl p-tolyl thioether 81, 85, 86, 90
TABLE IVERTING OF ETHER		Product	כוונים כוויכו	CII,0-()-Br	CII,0—()—CII,CI	CII,0-()-CII,CI	CIII,O—CII,O—NO,
		Parent Compound,	References, and tring t	p. Brumcanische, 24(80), 21(40), 27(80), 33(40), 87(60), 88(60)	o-Nitroni-ole 21, 23, 26(80), 11(06), 81, 85, 86, 89(08)	m-Nitroanisole	p-Nitrounisolo 21(70), 25, 24(76)

• Heferences 30-90 appear on p. 90. † Eigusse in parentheses indicate the per cent yields.

-COCH

2,4-Dimethylacetophenone 8(68) CILLO

Not mointed

Anisaldchyde 28(80) Acetophenone

CHOROMETHYLATION OF ALBERTHES AND KETONES

010

Salicylaldehyde 9, 38 ij

e-Homosalicylaldebyde

CHIC

Product

Parent Compound, References, and Yields † * References 50-90 appear on p 90 † Pigures in parentheses indicate the per cent yields

Ę,

CHIO

GIL

Acetomesitylene 8(77)

- 50 Vavon and Bolle, Compt. rend., 204, 1826 (1937).
- 51 Sommelet, Bull. soc. chim., [4] 15, 107 (1914).
- 52 Bert, Compt. rend., 186, 373 (1928).
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CHAPTER 4

THE AMINATION OF HETEROCYCLIC BASES BY ALKALI AMIDES*

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INTRODUCTION

Heterocyclic bases such as pyridine and quinoline and their derivatives react with metal amides to yield amino derivatives. For example, pyridine is converted to 2-aminopyridune by the action of sodium amide; an intermediate metal derivative is formed, and this is hydrolyzed to the free amine. (This reaction was discovered by Chichibhabin in 1914).

* The Chichibabin Reactions.

Chichibabin and Seide, J. Russ. Phys. Chem. Soc., 46, 1216 (1914).

It has been suggested ^{2, 2, 4} that the initial step in the reaction is the addition of the metal amide to the —CH—N— group; the resulting product is then transformed to the metal derivative of the amine, either through intramolecular rearrangement or through decomposition to the amino compound and sodium hydride which interact to give the metal derivative.

This mechanism accounts for the formation of small amounts of 4-aminopyridine (by 1,4-addition) and for the lack of formation of the 3-isomer. Evidence of the formation of an unstable addition product has actually been obtained for quinoline.⁵

THE SCOPE AND LIMITATIONS OF THE REACTION

The study of the amination of molecules containing the —CH=N—group has been confined almost entirely to the heterocyclic compounds. The few Schiff's bases (which also contain the —CH=N—group) which have been aminated in this way have given yields of 20% or less ^{2, 4} and the products are more readily synthesized by other methods. Of the heterocyclic bases only pyridine and quinoline and their derivatives give satisfactory results; amino derivatives of other heterocyclic bases such as pyrazines, pyrimidines, and thiazoles are not obtained readily by this reaction (see table). The amino derivatives of pyridines and quinolines, which are very difficultly available by other methods, are obtained directly in yields ranging from 50 to 100% by the use of alkali amides.

The more common methods of preparing aromatic amines, such as the reduction of nitro compounds, are generally of little value because of the difficulty in obtaining the desired intermediates. For example, nitration of pyridine with nitric acid is unsuccessful, and nitration with nitrogen peroxide (NO₂) gives a 10% yield of 3-nitropyridine. Other methods of synthesis of aminopyridines and aminoquinolines are illustrated in the following scheme.

² Ziegler and Zeiser, Ber., 63, 1848 (1930).

² Kirsanov and Ivaschenko, Bull. soc. chim., [5] 2, 2109 (1935).

Kirsanov and Polyakova, Bull. eoc. chim., [5] 3, 1600 (1936)

⁵ Bergstrom, J. Org. Chem., 2, 411 (1937).

⁶ Shoruigin and Topchiev, Ber., 69, 1874 (1936).

$$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} C_{1} \\ \end{array} \end{array} \end{array} \\ \begin{array}{c} \begin{array}{c} C_{1} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} C_{1} \\ $

The synthesis of 2-aminopyridine from the hydroxy derivative,7 as indicated above, results in over-all yields of less than 50%, and both this procedure and that involving the Hofmann degradation are long and tedious. The latter method is useful, however, for the preparation of 3-aminopyridines, which cannot be obtained by direct amination. The synthesis of 2-aminoquinoline derivatives from the alkali sulfonates is a convenient method when the corresponding 2-chloro derivatives are available. By contrast with these methods, the direct amination process is a convenient and economical one.

The case with which a substituted base undergoes amination is affected by the nature of the substitutents. When 2-alkylpyridines are treated with alkali amides in liquid ammonia, the only reaction observed is the formation of the salt of the enamic modification.10 but in hydrocarbon solvents at higher temperatures the 2-alkyl-6-aminopyridines are produced.11

If both the 2- and 6-positions are occupied by askyl groups, the amino group is forced into the 4-position. Thus, 2,6-dimethylpyridine and sodium amide in boiling xylene form 4-amino-2,6-dimethylpyridine.12

Fargher and Furness, J. Chem. Soc., 107, 690 (1915), Rath, Ger. pat., 510, 432 (1930). ¹ Camps, Arch. Pharm., 240, 317 (1902).

¹ Zerweck and Kunze, U. S. pat., 2,086,691 (1937); Ger. pat., 615.184 (1935).

¹¹ Bergstrom, J. Am. Chem. Soc., 53, 4065 (1931). 11 Seide, J. Russ. Phys. Chem. Soc., 50, 531 (1920).

¹¹ Chichibabin, J. Russ. Phys. Chem. Soc., 47, 835 (1915); Chichibabin and Vidonova J. Russ. Phys. Chem. Soc., 53, 238 (1921).

$$CH_3$$
 CH_3 + MNH_2 \rightarrow CH_3 NHM CH_3 + H_2

A study has been made of the effect of various substituents on the eourse of amination of the quinoline nucleus in liquid ammonia.12 In this solvent good yields of aminoquinolines are generally obtained, but, if an alkyl group is present in either positions 2 or 4, then salt formation occurs unless more vigorous conditions are employed. For example, 4methylquinoline is converted to 2-amino-1-methylquinoline when the reaction is earried out in dimethylaniline at 120°,14 but none of the product is obtained when the reaction is attempted in liquid ammonia at 20°.15 It might be expected that other salt-forming groups, such as amido, amino (aromatic), earboxyl, ethynyl, hydroxyl, imino, isonitroso, and active methylene groups, would exert the same effect on amination. This is not always true. Thus, a earboxyl group in the 2- or 4-position actually increases the rate of the reaction and improves the yield.13 2-Aminoquinoline-1-carboxylic aeid and 4-aminoquinoline-2-carboxylic acid are obtained in yields of 70 and 81% respectively from the corresponding acids, potassium amide, and potassium nitrate in liquid ammonia; under the same conditions, 2-aminoquinoline is obtained from quinoline in only 50% yield.12 On the other hand, an amino group in position 2 of quinoline prevents the amination, as does also a hydroxyl group in either position 2 or 8.13

When a sulfonic acid or methoxyl group is present in the 2-position of quinoline, it is replaced by an amino group by the action of potassium amide in liquid ammonia.¹³

Ordinarily the amination of pyridine and its derivatives can be controlled so that only one amino group is introduced. For example, from the reaction of pyridine with sodium amide in dimethylaniline at temperatures below 120°, 2-aminopyridine is obtained in yields of about 75%; 16 a small amount of the 4-isomer may or may not be formed.

¹² Bergstrom, J. Org. Chem., 3, 233 (1938).

¹⁴ Leffler, unpublished observations.

¹⁵ Bergstrom, J. Am. Chem. Soc., 53, 3027 (1931).

¹⁵ Schering A.-G., Ger. pat., 663,891 (1938).

When quinoline is treated with potassium amide in liquid ammonia, 2and 4-minoquinolines are formed in the ratio 5:1. Substitution of barhum amide for the potassium amide prevents the formation of the 4-isomer. It is probable that a similar result is not to be expected if the reaction is carried out in solvents other than liquid ammonia

Secondary reactions, in which the alkali salt of the aminoheterocyclic base acts as an aminating agent, are sometimes observed. Thus, dipyricylamine has been isolated as a by-product in the preparation of 2aminopyridine.¹³

$$\bigcap_{N = NHM} + \bigcap_{N} \rightarrow \bigcap_{N} \underbrace{M}_{N} + H$$

Quinoxaline is converted to fluorubin by potassium amide.20, 21

$$2 \underbrace{ N}_{N} + 2KNH_{1} \rightarrow 4H_{2} + \underbrace{ N}_{N} \underbrace{ K}_{N} \underbrace{ N}_{N} $

The only recorded attempt to produce a secondary amine by the reaction of substituted alkali amides with heterocyclic bases is the reaction of sodium phenylamide and pyridine; a small amount of 2-phenylamino-pyridine was obtained.

Another side reaction that takes place in the amination reaction is coupling. Bipyridy's are always produced in the preparation of aminopyridines. Thus, 2,2° bipyridy!, 4,4° bipyridy! and also dihydro-4,4° bipyridy! have been isolated as by-products in the amination of pyriding. 1° 18° 2. These products are often formed in significant quantities

W Shreve, Riechers, Rubenkoemg, and Goodman, Ind Eng. Chem., 32, 173 (1940).

¹⁴ Wibaut and Dingemanse, Rec. tras. chus., 42, 240 (1923).

Chichibabin and Seide, J. Burs. Phys. Chem. Soc., 50, 522 (1920).
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Berrstrom and Fernelius, Chem. Rev. 13, 162 (1933).

is Bergstrom and Fernelius, Chem. Rev., 12, 156 (1933).

when hydrocarbon solvents are employed but their formation is suppressed when the reaction is carried out in dialkylanilines.

The coupled products may undergo amination if the conditions of reaction are sufficiently strenuous. For example, 2,2'-bipyridyl is only slightly attacked by sodium amide in boiling tolucne but undergoes appreciable reaction in boiling xylene.23 The 4,4'-isomer is more readily aminated.24

Similar coupling products are formed from other heterocyclic bases 25 and are often the major products of the reaction between metal amides and complex heterocyclic substances.26

EXPERIMENTAL CONDITIONS

Direct amination is usually effected by treating the heterocyclic base with an alkali amide in the presence of a solvent. Potassium nitrate is often used to accelerate the amination of quinoline and its derivatives (see p. 100). The exact manner in which it functions is unknown but appears to be related to the oxidizing capacity of the nitrate ion.

The Alkali Amides. Many patents have been granted and much has been written about the preparation and properties of various metal amides, particularly of sodium amide.27 In the selection of the proper amide for any amination, the character of the compound to be aminated and the type of solvent to be used must be considered. On a manufacturing scale, the fact that sodium amide is much less expensive than other metal amides may be the determining factor.

Certain precautions must be rigorously observed in the handling of any metal amide. Most of the knowledge of this class of compound has been gained from the study of sodium amide, because of its wide use. It is especially important that the alkali amide be freshly prepared for each reaction. This is necessary, not only from the standpoint of the reproducibility of the experimental results, but also for reasons of safety. It has been shown a number of times 27 that alkali amides react with the oxygen, carbon dioxide, and water of the air to give dangerously explosive mixtures containing the hydroxides, carbonates, and nitrites. A patent has been granted to Ziegler 25 for the preparation of a homogeneous paste by grinding an alkali amide with several times its weight

²² Tjeen Willink, Jr., and Wibaut, Rec. trar. chim., 54, 281 (1935).

²⁴ Horsters and Dohrn, Ger. pat., 398,204 (1924).

²⁵ Chichibabin and Zatzepina, J. Rues. Phys. Chem. Soc., 50, 553 (1920).

²² Chichibabin and Shehukina, J. Rues. Phys. Chem. Soc., 62, 1189 (1930).

²⁷ For a review, "The Chemistry of Alkali Amides," see (a) Bergstrom and Fernelius Chem. Ret., 12, 43 (1933); (b) Bergstrom and Fernelius, Bid., 20, 413 (1937).

²² Ziegler, Ger. pat., 601,047 (1934).

of an inert liquid such as benzene. It is reported that such a paste can be handled and transported with safety. Even when stored under a dry hydrocarbon, an alkali amide should be carefully protected from the air and samples which develop a yellow or green or darker color should be discarded.

Sodium amide is employed in most aminations except those in which liquid ammonia is used as the solvent. Because of its insolubility in liquid ammonia, it is inferior to potassium or barium amide, both of which are soluble. Wibaut and Dingemanse is found that an especially pure sodium amide is failed to react with pyridine under conditions which were very estisfactory when a commercial grade of sodium amide was used.—This and other reports indicate that the amination is influenced by impurities, probably the substances used as eatalysts in the preparation of the amide (p. 99).

The Solvent. Various hydrocarbons (such as benzene, toluene, xylene, cumene, mesitylene, and petroleum fractions), dimethylaniline, diethylaniline, and liquid ammonic have been used as solvents. The amination of pyridine in the absence of a solvent is also successful. With quinolines and isoquinolines good yields are obtained in liquid ammonia solution, his but, since the reactions must be carried out at room temperature or above, special apparatus must be used to prevent the development of dangerous pressures due to the hydrogen evolved. The yield of 2-aminopyridine obtained in reactions employing liquid ammonia as a solvent is less than 30%. By the use of hydrocarbon solvents such as toluene, yields as high as 36% of this product have been reported; however, it has been the general experience of several workers him that the nure material is usually obtained in yields of 50% or less.

The introduction of dialkylanilines ¹⁶ u as solvents has greatly increased the practical value of amination of pyridine and its homologs. For example, 2-aninopyridine is obtained in 70-80% vibels from pyridine and sodium amide in dimethylaniline at 90-115°, and 2,6-diamino-pyridine in yields of 80-90% at 150-180°. It is probable that the value of dimethylaniline and diethylaniline "depends on their solvent action on sodium amide and on the sodium amide-pyridine addition compounds. Unfortunately, the investigation of these solvents in aminations of heterocyclic bases other than pyridines has been very limited.

Temperature. An amination should be carried out at the lowest temperature which will promote the desired reaction. In monoaminations this is usually the temperature at which a steady evolution of

¹⁹ Titherley, J. Chem. Soc., 65, 504 (1894).

³² Vieweg, Ger. pat., 476,458 (1929).

¹¹ Ostromislensky, J. Am. Chem. Soc., 56, 1713 (1934).

hydrogen occurs. Temperatures higher than necessary are to be avoided because of increased diamination, coupling, etc. For the preparation of monoaminopyridines the temperatures reported are usually in the range of 100-150°. Aminoquinolines have nearly always been prepared in liquid ammonia at room temperature.

Mole Ratio. In the preparation of monoaminopyridine in the presence of dialkylanilines, the alkali amide is used in about 25% excess over the theoretical amount.16, 14 In the older experiments using hydrocarbon solvents the ratio of amide to pyridine was usually 2: 1, and because of the large excess of amide there was often pronounced conversion to diamino derivatives and coupled products. In the amination of pyridine without a solvent, it is recommended that the amide be used in the amount theoretically required for the introduction of the desired number of amino groups.17

General Precautions. The reagents and apparatus employed should be dried. In laboratory preparations it is advisable to use the alkali amide in the flask in which it is prepared, thus avoiding possible exposure to the air in transferring the material. Apparatus should be earefully washed with alcohol or dilute aqueous sodium hydroxide, after the reaction is complete, to prevent the formation of explosive mixtures from any remaining alkali amide.

EXPERIMENTAL PROCEDURES

Preparation of Sodium Amide

Sodium amide is prepared on a commercial scale by the action of dry ammonia on molten sodium at 350°. Because of the slowness of the conversion, various catalysts, such as sodium hydroxide, sodium oxide, and oxides of chromium or related metals,27 are usually added, and samples of the commercial material may be expected to contain varying amounts of one or more of these substances.

The procedures described in Organic Syntheses 22 and Inorganic Syntheses, 22 involving the use of gaseous ammonia and molten sodium. are quite adequate in detail and are satisfactory when large quantities of the amide are desired. However, for use in ordinary laboratory operations, the amide is more conveniently prepared by the liquid ammonia process described below. This method has the further advantage of allowing the amination to be carried out in the same flask in which the amide is prepared. The method may also be adapted to the preparation of small amounts of potassium amide.

²² Bergstrom, Org. Syntheses, 20, 86 (1940).

Dennis and Brown, Inorg. Syntheses, 1, 74 (1939).

Procedure. A 500-cc. three-necked flask is equipped with a gastight mechanical stirer, a bubbling tube, and an outlet tube attached to a wide-bore soda-lime tube. Approximately 250 cc. of liquid ammonia from a tank is collected in the flask, and 0.15 c. of ferric nitrate (anhydrous or hydrated) is added. About 0.5 c of clean sodium is then added, and after it has dissolved the solution is stirred and dry air is slowly bubbled in until the blue color has dissupeared. The oxide so formed acts as a catalyst in the subsequent reaction. The bubbling tube is removed and 11.5 g. (0.5 atom) of clean sodium is added to the stirred solution in portions sufficiently small to prevent vigorous reaction. The mixture is stirred for fifteen to twenty minutes after the addition of the sodium is complete.

If the amide is to be used in a solvent other than ammonin, the animonin is allowed to evaporate while the new solvent is slowly added from a dropping funnel. If the dry amide is desired, the product may be freed from ammonia by evacuation at 100°. In any event, sodium amide prepared by this method must be used immediately Because of its finely divided condition and the presence of oxides, it rapidly changes to explosive substances.

Preparation of 2-Aminopyridine 14. 14, 21

The flask containing the suspension of sodium amide in liquid ammonia (preceding paragraph) is fitted with a small dropping funnel, and 45 cc. of dry dimethylaniline is added cautiously, the ammonia being allowed to escape through the soda-lime tube. After all the ammonia has been driven out, the soda-lime tube is removed and a dry vertical condenser. protected by a calcium chloride tube, is attached. The mixture is stirred and 31.6 g. (0.4 mole) of dry pyridine is added through the dropping funnel. The funnel is then replaced by a thermometer which dips into the reaction mixture. The flask is beated in an oil bath, the temperature of the reaction mixture being maintained at 105-110° until the evolution of hydrogen has ceased. Hydrogen is produced rapidly at first, as shown by the continuous stream of bubbles observed when a rubber tube connected to the calcium chloride tube is dipped under water. After eight to ten hours the formation of hydrogen is negligible. Near the end of this period it may be necessary to discontinue the stirring because of the formation of a solid cake in the reaction flask.

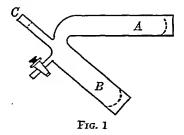
When the reaction is complete, the mixture is cooled and 6% aqueous sodium hydroxide solution (about 75 cc.) is gradually added until the vigorous decomposition has stopped. Water (about 300 cc.) is then

⁵⁴ Vaughn, Vogt, and Nieuwland, J. Am. Chem. Soc., 55, 2120 (1934).

added to complete the hydrolysis of the sodium salt. The mixture is extracted with 75 cc. of petroleum ether (b.p. 30-60°) to remove the dimethylaniline; if necessary more water may be added to assist in the separation of the layers. The aqueous solution is cooled to 15°, saturated with solid sodium hydroxide, and extracted several times with benzene. The combined benzene extracts are dried over anhydrous sodium sulfate, and the residue from the distillation of the solvent is distilled under diminished pressure. The product boiling at 117-120°/36 mm. weighs 23-28.6 g. (66-76%). The residue consists of 4,4'-bipyridyl, 2,2'-dipyridylamine, and other unidentified products.¹⁷

Preparation of 4-Amino-2-phenylquinoline 25

In leg A of the two-legged tube (Fig. 1) are placed 1.05 g. (0.027 atom) of potassium and 0.02 g. of ferric oxide. Tube C is closed with a stopper, and legs A and B are sealed off as indicated by the dotted lines while a



stream of ammonia is passed in through the stopcock. Through tube C 1.83 g. (0.0089 mole) of 2-phenylquinoline and 1.61 g. (0.016 mole) of potassium nitrate are introduced into leg B. Tube C is then sealed off as indicated. At intervals ammonia is condensed in leg A, by cooling A in a solid carbon dioxide-acetone bath, until the rapid conversion of potassium to potassium amide is complete. Hydrogen is occasionally vented during this operation. Ammonia is then condensed in the apparatus until 15–20 cc. is present and the contents of the tubes are mixed thoroughly by shaking. The apparatus is allowed to stand at room temperature, with the stopcock closed, for four hours.

The ammonia is evaporated from the reaction mixture and the contents of the tube are rinsed out with ethanol and benzene. Water is added to the mixture, and the greater part of the organic solvents is removed by distillation. The 4-amino-2-phenylquinoline which separates is collected by filtration. The dry, nearly pure product weighs

²⁵ Bergstrom, J. Org. Chem., 3, 424 (1938).

1.96 g. (99.7%). After recrystallization from benzene or dilute ethanol, it melts at 164-165°.
Rups of larger six should not be attempted in the apparatus described.

Runs of larger size should not be attempted in the apparatus described.

Apparatus for larger runs has been devised.

**The content of the co

SUMMARY OF AMINATIONS OF HETEROCYCLIC BASES (TABLE)

In the table are summarized the aminations of heterocyclic bases reported prior to January 1, 1941. It is possible that many of the yields recorded in the table, particularly in connection with preparations in which hydrocarbon solvents were used, might be improved by carrying out the reactions in dimethylandine solution.

M Bergstrom, J. Org. Chem., 2, 423 (1937).

ΤΛΒΙΕΕ Πετεποσγείες Βλπές Αλιυκτέρ ητ Αξέλει Ανίθεθ

Hoterocyclic Base	Alkali Amido	Solvent and Temperature	Amino Heterocyclic Ba o	Yield, C.	Yield, C. Reference
Acridino	KNII3	Ammonia	9-Amívoaeridine		*
	Ba(NH5)2	Ammonia	9. Aminoacridine		: ·
2,2'-13ipyridyl	NaNIL	Tolucue, 110	(?)-Diamino-2,2'-bipyridyl	Poer	23, 38
4,1'-Bipyridyl	NANII,	Cumene, 200°	2,2'-Diamino-4, f'-bipyridyd		.
Isoquinolino	KNII	Ammonia, 25°	1-Aminoi-equinoline	3	33°, E9
Isoquinoline-1-carboxylic	KN115	Аппонія	1-Aminoi>aquinolin^1-earboxylic acid		
Phenon(hridino	NaNIIs	Nylene 110-130°	6. Aminophenanthridine	5-5	21
	KNII	Ammonia	6-Aminophenanthridine	8.	Ę
6-Phenylphenanthridine	KN112 or Ita (N112), Ammonia	Ammonia	te. Aminophenanthridine		22
Pyrazino	KNII	Ammonia	No preducts i-clated		e E
2,5-Dimethylpyrazino	NnN113	Nylene	3-Amino-2, 5-dimetby hyracino	Pont	ä
Pyridino	NaNII	Dimethylaniline 100-115	2-Aminopyridine	57	10, 41
	2NaNII;	Dimethylaniline 170°	2,6-Diaminopyridine	8-38	16, 15
	3NuNII.	Dimethylaniline	2, 1, t-Triaminopyridine		9
2,t&Dimethylpyridine	NaNIIs	Toluene	4-Amino-2, dedinethy hyridine		2
4-18thylpyridino	NaN II	Hydrocarbon, 150°	2-Amino-Fethylpyriding		17
5-18thyl-2-methylpyridino	NaNH ₂	Hydroearbon, 150.	6-Amino-Sethyl-2-methylpyridina	-	끄
3-Hydroxypyridino	NuNII	p-Cymeur, 210°	2,0-Diaminopyridine		2
2-Methylpyridine	NaNII3		t-Amino-2-methylpyridine		<u></u>
2-Mothylpyridine	NaNII3	200°	L&Dimino2-methylyyridine		<u> 2</u>
3-Methylpyridina	NaNIIs	Nylene 135-1-10	2-Amino-3-methylpyridine	E.	ş
4-Methylpyridine	NaN 11,		2-Amino-1-methylpyridine		3
3-(2'-N-Methylpiperidyl)-	NuN113	Nylene (reflux)	a-Amme-(and a amino)-N-methyl-	-05-05	51
Dyrating			nucleation		
(18-Methylmhame)					

	or thinks	«-Aminonicotne	88
Α_	Dimethylaniline	2-Ammornabasine	3 9
200	200	4,6-Diamino-2-propylpyridine	2
_		pyrimidine	
	Ammonis, 30-70-	2-Aminoquinoline and	8 £
Am.	Ammonia, 25*	2-Ammoquinolme	2
V III	Ammonia, 25*	2-(7)-Amino-5,6-benzoquinoline	8
Ā	Ammonta, 25°	2-(?)-Amino-7.8-benzoquinoline	8
Amp	Ammonia, 25*	4-Amino-2-carboxyquinoline	25
4	Аттова, 25°	2-Amino-4-carbonyquinoline	Ę.
Атото	Ammonia, 25°	(?)-Amino-Gearboxyquinoline	8
Amm	Ammonia, 25°	(?)-Amino-6-dimethylaminooninging	7
Amm	Ammonia, 25°	(?)-Amino-8-ethoxyqunoline	_
Ding.	Dimethylandine 115-125°	2-Amino-4-methylquinoline	46
Amm	Ammonia, 25°	(?)-Aramo-6-methylquinoline	25
Y	Ammonia, 23	Onsuccessful	0
Amme	Ammonia, 25*	2-Aminoconingford	8:
Amme	Аштопа, 25°	(?)-Amno-6-methoxyminolina	10 27
T V	Ammonia, 25°	4-Amino-2-phenylquinoline	92-100

HETEROCUCIES BISES AND THE DAY

TABLE-Continuel

Hetenocyclic Basis Ambathe of Alkali Ampes

Heterocyclic Base	Alkuli Amide	Solvent and Temperature	Amino Heterocyclic Bwo	Yie41,52	Yeld, C. Reference
6-Phenylquinoline 8-Phenylquinoline 2-Sulfoquinoline 6-Sulfoquinoline Quinaxaline 2,3-Dimethylquinoxaline 2,3-Dimethylquinoxaline	Na(NII2)2 Ba(NII3)3 KNNII3 Ba(NII3)3 KNNII2 KNNII2	Ammonia, 25°	(2)-Annino-G-phenylquinolino (7)-Amino-S-phenylquinolino 2-Aminoquinolino (2)-Amino-G-culfoquinolino Fluorulin (K alt) Dipotassium salt	2322	*
quinoxaline 2,3-Diphenylquinoxaline 2,3-Diphenyl-6-methyl-	KNII.	Ammonia, 130-140° Ammonia, 130-140°	2-Amino-3-phenylquinoxaline 2-Amino-6-methyl-3-phenylquinoxa- line	programment of the Sta	ម្ភ ខេ ម
quinoxalino 6-Methylquinoxaline 4-Methylthiazolo	KNII, NaNII,	Ammonia 150°	2-Amino-t-methylthiarelo	a bath has shring an angalogs, dan say	SS.
37 Reference 27q. p. 163.			4 Soith, J. Russ, Phys. Chem. Sec., 50, 534 (1920).	t (19.50).	Control of the following special speci

	Bull. sec. chim., [5] 2, 570 (1935).
37 Reference 27a, p. 163.	39 Kabatchnik and Katzelsohn, B

⁴⁰ Chichibabin and Oparina, J. Russ. Phys. Chem. Soc., 50, 543 (1920). 4 Bergstrom and Rodda, J. Am. Chem. Noc., 62, 3030 (1910). 39 Bergstrom, Jinn., 515, 31 (1931).

4 Plazek, Roczniki Chem., 16, 403 (1936).

" Schoolderwirth, U. S. 1741, 2,084,540 (1975).

" Yards, 18ca., 57, 18th (1924).

⁴ Morgan and Walls, J. Chem. Soc., 2229 (1932).

⁴³ Reference 27b, p. 472.

⁴ Reference 27a, pp. 151-158; 5b, p. 463,

⁴ Philipp, U. S. pat., 1,789.022 (1931).

HOchiai, J. Pharm. Sv. Japan, 58, 1010 (1938). 18 Reference 27a, p. 162.

[&]quot; Menschikov, Grigmmutch, and Orecheff, Rec., 67, 209 (1934). 4 Ochiai and Karai, J. Phorm. S & Japan, 59, 18 (1930). ¹³ Chelnibabin and Kirranov, Rev. 57, 1163 (1921). 13 Soids, Res. 57, 791 (1924).

¹⁴Opg and Bergetmus, J. Am. Chem. Sec. 53, 1849 (1931).

CHAPTER 5

THE BUCHERER REACTION

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INTRODUCTION

The Bucherer reaction is the reversible conversion of a naphthylamine to a naphthol in the presence of an aqueous sulfite or bisulfite. It has proved to be of value in the synthesis of naphthalene derivatives, particularly in the manufacture of dye intermediates. In certain instances it is conveniently used in the preparation of naphthols from naphthylamines; in others it is employed for the reverse transformation, the synthesis of naphthylamines from naphthols.

(1)
$$\begin{array}{c} NH_2 \\ + H_2O \xrightarrow{N_3H\otimes O_2} \\ \hline \\ SO_2H \\ \end{array}$$

$$\begin{array}{c} OH \\ + NH_2 \\ \hline \\ \end{array}$$

$$\begin{array}{c} OH \\ + NH_2 \\ \hline \\ \end{array}$$

$$\begin{array}{c} OH \\ + NH_2 \\ \hline \end{array}$$

$$\begin{array}{c} OH \\ + NH_2 \\ \hline \end{array}$$

The second reaction has been extended to the synthesis of certain alkyland aryl-aminonaphthalenes by the use of alkyl- and aryl-amines and sodium bisulfite, to the synthesis of naphthylhydrazines by the use of hydrazine sulfite, and to the synthesis of carbazoles by the use of phenylhydrazine and bisulfite.

Although Lepetit 1, 2 was the first to discover the amazingly easy transformation of naphthionic acid to 1-naphthol-1-sulfonic acid (equation 1), Hans T. Bucherer 2 discovered the reaction independently, recognized its usefulness, and demonstrated its reversibility. As a consequence, the name Bucherer has continued to be associated with these transformations.

MECHANISM

Studies of the mechanism of the formation of a naphthylamine from a naphthol, sodium bisulfite, and ammonia indicate that the reaction involves addition of the bisulfite to the keto form of the naphthol.

(3)
$$OH = OH$$

$$NH_{2}$$

$$NH_{2}$$

$$SO_{2}Na$$

$$NH_{2} + (NH_{4})N_{2}SO_{2}$$

The reaction of the addition product with ammonia is similar to that of the sodium bisulfite addition product of formaldehyde, which yields sodium aminomethanesulfonate.⁵ Compounds similar to the bisulfite

Lepetit, pli cacheté No. 858, May 16, 1896; Bull. roc. ind. Mullouze, 326 (1908).
 Friedländer, Ber., 54, 629 (1921).

² Bucherer, J. praid. Chem., [2] 69, 49 (1994).

Fushs and Stir, Ber., 55, 658 (1922).
 Raschig, Ber., 59, 859 (1920).

addition product pictured in (3) have been isolated from hydroquinone, resortion!, phloroglucinol, disodium 2-naphthol-1-sulfonate, 2,7dihydroxynaphthalene, 1,5-dihydroxynaphthalene, 4 and many other substances. In some instances the action of bisulfite leads to the introduction of sulfonate residues in addition to the one on the carbonyl carbon, 4-6.7.

The mechanism of the Bucherer replacement of an amino group by a hydroxyl group is well illustrated by the behavior of naphthionic acid and sodium bisulfate. After naphthionic acid has been boiled for some time with a 40% solution of sodium bisulfate and the mixture has been made acid to Congo paper and boiled to exped excess sulfur dioxide, a small quantity (ca. 15%) of 1-naphthol-sulfonic acid can be isolated. The remainder is present as addition product (cf. reaction 3). If this mixture is now made alkaline to phenophthalcie and boiled, ammonia to driven off and disodium 1-naphthol-1-sulfonic is produced. When the resultant mixture is again acidified to Congo paper and boiled, more sulfur dioxide is removed and the remainder of the starting material can be accounted for as 1-naphthol-1-sulfonic acid. It is apparent that the intermediato bisulfite addition product is quite stable toward dilute acid but is readily decomposed by alkali.

II, after the excess bisulate has been decomposed as above, the resulting mixture is heated with excess ammonia, the original naphthionic and is regenerated. The papers of Fuchs and co-workers * 1. 1. 1. 2 describe the properties of a variety of such addition products.

SCOPE OF THE BUCHERER REACTION

The replacement of hydroxyl by amino groups, or of amino by hydroxyl groups, is limited practically to analyticalene derivatives and resorcinol. Benzene derivatives containing one hydroxyl or one amino group are much less reactive than similar naphthalene derivatives. Polyfunctional hearners rate more readily, but with the exception of resorcinol they undergo reactions which are complicated by secondary processes. Hydroxyanthraquinones do not react.

Dihydroxy or diamino derivatives of naphthalene in which the substituents are in different rings usually undergo replacement of only one of the two groups; the second group may, however, be involved to a limited extent (cf. behavior of naphthals with hydrazine sulfite and

^{*} Fuchs and Elsner, Ber., 52, 2281 (1919).

Fuchs and Elsner, Ber., \$3, \$86 (1920).

Fuchs, Ber., \$4, 245 (1921).
Woroshirow, Ber., \$2, 57 (1929).

^{*} Fuchs and Pirsk, Ber., \$9, 2458 (1926).

hydrazine, p. 114). For example, 1,5-diaminonaphthalene, heated under reflux with sodium bisulfite solution,³ is slowly converted into an addition product which, after destruction of the excess bisulfite, can be salted out in considerable quantity. This addition product is converted into 1-amino-5-naphthol by heating with alkali. Concurrently with the production of this addition product, a small amount of the addition product of 1,5-dihydroxynaphthalene is formed, and it, too, can be salted out (it is more sparingly soluble than the one previously mentioned). A small quantity of free aminonaphthol and dihydroxynaphthalene as well are formed during the reaction. The total yield of aminonaphthol is about 80%.

Conversion of Amines to Hydroxyl Compounds

Reactions of Primary Amines. Both α - and β -naphthylamines can be converted to naphthols in practically quantitative yields. Addition products are first formed, and these are decomposed by treatment with alkali, although a varying, usually small, amount of the addition product decomposes during the first stage of the preparation. Most substituted naphthylamines (except those having an N-aryl substituent) also react within the limitations discussed below. Naphthylamine- and aminonaphtholsulfonic acids are important dye intermediates, and the application of the Bucherer reaction to these compounds has been studied extensively.

The effect of various experimental conditions on the conversion of sodium 1-amino-5-naphthalenesulfonate to the corresponding naphthol has been studied by Kogan, 10 who found that the reaction proceeded best in a slightly acid solution with about seven moles of bisulfite per mole of aminonaphthalenesulfonate.

The effects of a sulfonic acid group on the replacement of the amino group by hydroxyl may be summarized as follows.

- (a) A 1,4-relationship of amino group and sulfonic acid group promotes the reaction.
- (b) A 1,2-, 1,3-, or 2,3-relationship of the same groups hinders the reaction.
- (c) A relationship such that the two groups are in different rings has little effect on the ease with which the reaction takes place.

Because of the effect of the position of a sulfonic acid group on the reactivity of the amino group, the Bucherer reaction of diaminonaphthalenesulfonic acids often takes only one of two possible courses. For

¹⁹ Kogan and Nikolaeva, J. Applied Chem. (U.S.S.R.), 11, 652 (in French 659) (1938) [C. A., 32, 7031 (1938)].

example, 1,8-diaminonaphthalene 1-sulfonic acid is easily converted into

8-amino-1-naphthol-1-sulfonic acid, rather than into 8-hydroxy-1-naphthylamine-1-sulfonic acid.

Similarly, 1,5-diaminonaphthalene-1-sulfonic acid yields 5-amino-1-naphthol-1-sulfonic acid.

$$\underbrace{\begin{array}{c} NH_{2} \\ NH_{2} \end{array}}_{NH_{1}}\underbrace{\begin{array}{c} NH_{2} \\ H_{2}O \end{array}}_{NH_{2}}\underbrace{\begin{array}{c} OH \\ NH_{2} \end{array}}_{NH_{2}}\underbrace{\begin{array}{c} OH \\ NH_{2} \end{array}}_{NH_{2}}$$

However, if the amino group at position 1 is acetylated, then the amino group in position 5 takes part in the reaction.

Evidently the acetyl group is removed by hydrolysis after the Bucherer reaction is complete, for the product is the free amine.

The hindering effect of a sulfonic acid group on the replacement of an adjacent amino group is seen in the reaction of 1,5-diaminonaphthalene-2-sulfonic acid; the product is 1-amino-5-aaphthol-2-sulfonic acid.

Occasionally secondary amines are formed as hy-products of the Bucherer reaction with naphthylamines. For example, treatment of 2naphthylamine-5-sulfonic acid with even a brige excess of sodium bisulfies (10-20 moles) leads to a mixture containing the dinaphthylaminesulfonic acid as well as 2-naphthol-5-sulfonic acid, but even after long heating demonstrable quantities of the original naphthylaminesulfonic acid are present.¹¹ This behavior is obviously a result of reaction between the

¹¹ Bucherer and Stohmann, J. pratt. Chem., [2] 71, 433 (1905).

addition complex and the amine and corresponds to the reaction type discussed below.

$$\begin{array}{c|c} & \text{NH}_2 & \text{NaHSO}_2 \\ \hline & \text{SO}_2\text{H} & \\ \end{array} \begin{array}{c} & \text{SO}_2\text{H} \\ \end{array} + \begin{array}{c} & \text{NH} \\ & \text{SO}_2\text{H} \\ \end{array}$$

Reactions of Secondary and Tertiary Amines. N-Mono- and N,N-dialkyl derivatives of naphthylamines can be converted to naphthols by treatment with aqueous sodium bisulfite. These reactions frequently take place with greater ease than those of primary amines. In the case of the N-monobenzyl derivatives of 1-naphthylamine-1,7- and -4,8-disulfonic acids the yield of benzylamine varies from 60 to 77%. In the case of N-monobenzyl-1-naphthylamine-4-sulfonic acid the yield of benzylamine is smaller and the time for conversion longer; one would anticipate a ready cleavage because of the activating effect of the sulfonic acid group, but the sparing solubility of the compound hinders the reaction. The disulfonic acid, which is more soluble, reacts more readily. Apparently the N,N-dibenzyl derivatives of the same compounds are not cleaved at all under comparable conditions or even by heating in a closed container at 125-150°.13

Conversion of Hydroxyl Compounds to Amines

Preparation of Primary Amines. 1- and 2-Naphthols and their derivatives can be converted into primary amines by treatment with ammonia and ammonium sulfite or by the action of ammonia on their bisulfite addition products.¹³ The effect of substituents on ease of replacement is the same as that mentioned above. Hydroxyquinolines may be aminated similarly.¹⁴

Inasmuch as 2-nitronaphthalene cannot be obtained by direct nitration, the Bucherer process for preparing 2-naphthylamine and its derivatives is of considerable importance. In the preparation of 2-naphthylamine from 2-naphthol, reaction begins around 100° but proceeds much more rapidly in an autoclave at about 150°. Yields given range from 88% ¹⁵ to "practically quantitative." Other references to 2-naphthylamine will be found under C₁₀H₉N in the table of compounds prepared by the Bucherer reaction on p. 122. An advantage of the Bucherer method for the preparation of 2-naphthylamine is that the process can be carried out at a temperature such that there is practically

¹² Bucherer, J. prakt. Chem., [2] 70, 345 (1904).

¹³ Bucherer and Seyde, J. prakt. Chem., [2] 75, 249 (1907).

¹⁴ Woroshtzow and Kogan, Ber., 65, 142 (1932).

¹⁵ Bezzubetz, J. Chem. Ind. (Moscow), 7, 998 (1930) [C. A., 25, 4545 (1931)].

no formation of 2-2'-dinaphthylamine; 2-naphthylamine is filtered from the cooled reaction mixture, and the mother liquor can be used again 3

the cooled reaction mixture, and the mother liquor can be used again.\(2.8\text{-Dihydroxynaphthalene-6-sulfonic acid, "G acid," is converted to 2-mino-8-naphthol-8-sulfonic acid in 80% yield.\(\) Similarly, 2,5-dihydroxynaphthalene-7-sulfonic acid yields 2-mino-5-naphthol-7-sulfonic acid, and 1,5-dihydroxynaphthalene-7-sulfonic acid yields 1-amino-5-naphthol-7-sulfonic acid. In these instances the hindering effect of the sulfonic acid group causes the reaction to take place in the other ring.

The behavior of 2-hydroxy-3-naphthoic acid in the Bucherer reaction is worthy of note. This acid undergoes decarboxylation below 100° when heated in the presence of aqueous sodium bisulfite, although the acid itself can be heated in water for cighteen hours at 125° without change.14 When heated with ammonia and ammonium sulfite at 150-155° for nine hours it is converted into 2-naphthylamine (67%) and 2,2'-dinaphthylamine (23%). The bisulfite addition product of 2hydroxy-3-naphthoic acid is related to a 8-keto acid; the decarboxylation is therefore to be expected. The observed is stability of ethyl 2-hydroxy-3-naphthoate toward boiling sodium bisulfite solution is understandable: no loss of carlon dioxide would be expected even though the bisulfite addition product of the keto form were produced, for 8-keto esters are quito stable. Bucherer's experiments do not prove whether or not the bisulfite addition product of the keto ester is formed, but they do demonstrate that replacement of the 2-hydroxyl group by an amine group does not occur. The hindering effect of the carbethoxy group is thus to be compared with the similar influence of the sulfonic acid group.

8-Hydroxyquinoline is converted "almost quantitatively" into 8aminoquinoline by heating with ammonia and armonium sulfite in a closed vessel at 150-160° for six to seven hours. "6-Hydroxyquinoline and 8-hydroxyquinoline-5-sulfone acid are similarly converted to the corresponding aminominolines.

Preparation of Secondary Amines. Conversions of naphthols to N-alkyl- or N,N-dialkyl-aminoanphthalenes require more vigorous conditions than are nere-sery for the production of primary amines by means of ammonia and ammoniam sulfite. For example, amination of l-naphthol-I-sulfunic acid takes place smoothly at 90°, but the substitution of methylamine for ammonia necessitates earrying out the process at 150° in an autoclave. It is possible in such instances to heat together one mole of amphthol, one mole of alkylamine sulfite, and one mole of alkylamine in an autoclave at 126°-150° until reaction is complete (test for residual amphtholsulfonia acid), or to prepare the addition product from the haphthol and excess solium bi-sulfite and, after addification

¹ Bucherer, Z. Farb. Text. Chem., 1, 477 (1903).

and expulsion of sulfur dioxide by heating, to heat the addition product with two moles of amine. The excess amine can be recovered in either case. Numerous examples of this process involving ethanolamine, ethylenediamine, methylamine, etc., are to be found in the patent literature.^{17, 18, 19, 20}

The introduction of arylamino residues occurs more readily with naphthols of the β-series ¹¹ (see also the next section). 1-Naphthol-½-sulfonic acid does not react with aniline and sodium bisulfite at 100°, but 2-naphthol-6-sulfonic acid reacts smoothly at this temperature, yielding 2-phenylaminonaphthalene-6-sulfonic acid. ^{11, 21, 22} The corresponding 2-phenylamino-8-sulfonic acid has been prepared in a similar manner. ^{21, 22} The yield of 34% (recrystallized product) obtained after boiling for nineteen hours could undoubtedly be increased by operation at a more elevated temperature in an autoclave provided with a stirrer.

$$HO_3S$$
 $OH \xrightarrow{C_6H_5NH_2} HO_3S$
 NHC_6H_5

There is wide variation in the tendency of aromatic amines to undergo this reaction. The table below lists a number of common amines in the order of increasing reactivity toward β -naphthols.

REACTIVITY OF SOME ARYLAMINES IN THE BUCHERER AMINATION PROCESS II

Relatively unreactive Benzidine

β-Naphthylamine Aminonaphthol ethers

Xylidine

o- and p-Toluidine

Aniline

Moderately reactive p-Phenetidine

Sulfanilie acid Metanilic acid

Extremely reactive p-Aminophenol p-Phenylenediamine

Later work 2012 has shown that arylamination may be extended to

¹⁷ Brit. pat., 249,717 [C. A., 21, 916 (1927)].

¹⁵ Brit. pat., 436,805 [C. A., 30, 2203 (1936)].

¹⁹ U. S. pat., 1,543,569 [C. A., 19, 2345 (1925)].

²⁰ Fr. pat., 788,707 [C. A., 30, 1586 (1936)].

Bucherer, Z. Farb. Text. Chem., 3, 57 (1904).
 Bucherer, Z. Farb. Text. Chem., 2, 193 (1903).

²²² U. S. pat., 2,059,466 [C. A., 31, 418 (1937)].

1-naphthols under special conditions. The salt of an arylamine will react at a temperature between 100° and 200° with a molecular equivalent of the isolated bisulfite addition product of a 1-naphthol; the product, an arylaminonaphthalene, is formed in good yield. The reaction may also be carried out in aqueous solution; the bisulfite addition product is prepared in the usual way in aqueous medium, excess bisulfite is neutralized or removed by acid, the requisite amount of amine hydrochloride is added, and the mixture is heated in an autoclave. It has been surgested 224 that the intermediate involved is a salt of the addition product and the amine

In many cases it is possible to isolate such saltlike addition products. which, on heating, yield the expected amine, sulfur dioxide. and water

The usefulness of any particular arylamine in the Bucherer process is determined not only by its own tendency to enter the reaction but also by the reactivity of the bisulfite addition compound of the naphthol with which it is being condensed. p-Toluidine in the presence of bisulfite does not react rapidly with 2-naphthol-6-sulfonic acid; however, the yield is practically quantitative when the isomeric 2,8-acid is used." Likewise, benzidine, which reacts with β-naphthols only with extreme difficulty, reacts much more readily with 2-hydroxy-3-naphthoic acid and with 2,8-dihydroxy-3-carboxynaphthalene-6-sulfonic acid. both of which are notable for the case with which they undergo amination by

It is possible to use relatively complex amines in this process. Thus p-rosaniline reacts readily in the presence of sodium bisulfite with 2naphthol-6-sulfonic acid to form substituted rosanilines. In II The exact constitution of the reaction products has not been established.

The effects of substituent sulfonic acid groups in the naphthol nucleus upon the ease of reaction with an arylamine are identical with those mentioned earlier (p. 108).

Preparation of Secondary Amines from Primary Amines

2-Naphthylamines can be substituted for 2-naphthols in any of the reactions described on pp. 110-113; 1-naphthylamines can be substituted for 1-naphthols only in those processes involving alkylamination or dialkylamination. The 2-naphthylamines react more easily than the corresponding naphthols.¹¹ Thus 1-methylamino-7-naphthol-4-sulfonic acid can be prepared from 1-amino-7-naphthol-4-sulfonic acid by treatment with sodium bisulfite and methylamine.²² Likewise, 2-(4'-hydroxy-phenylamino)-naphthalene can be prepared from 2-naphthylamine and p-aminophenol,²⁴ and 2-phenylaminonaphthalene-6-sulfonic acid can be prepared from 2-aminonaphthalene-6-sulfonic acid.¹¹⁻²¹

2-Amino-8-naphthol-6-sulfonic acid, 2-aminonaphthalene-6,8-disulfonic acid, and 2-amino-5-naphthol-7-sulfonic acid all react in the presence of sodium bisulfite with *p*-rosaniline to form substituted rosanilines.¹¹

The process discussed above may be summarized as follows.

$$\begin{array}{ccc} \text{ArNH}_2 & \xrightarrow[\text{ReNH}]{\text{NaHSO}_2} & \text{ArNHAr' or ArNR}_2 & & \text{(R = alkyl or hydrogen)} \\ & & \text{ReNH} & & \end{array}$$

It should be noted that no useful reversal of the Bucherer reaction takes place when N-aryl-2-naphthylamines are heated with sodium bisulfite solution.

Reactions Involving Hydrazines

Arylhydrazines are formed in the reaction of hydrazine sulfite and hydrazine with naphthols.^{25, 26, 27} Thus hydrazines can be prepared from 1- and 2-naphthol, and 2,7-dihydroxynaphthalene yields 7-hydroxy-2-naphthylhydrazine (82%) with a very small amount of dihydrazine under the conditions used.²⁶ Both hydroxyl groups of 2,3-dihydroxynaphthalene can be replaced by hydrazine residues; ²⁶² the yield of crude product is about 57%. Similarly resorcinol yields m-phenylenedihydrazine.²⁶² The latter compound cannot be isolated as such but can be obtained as its reaction product with benzaldehyde (yield 50%). Pyrocatechol, hydroquinone, 3,4-diaminotoluene, and salicylic acid do not undergo the reaction.²⁶² It is to be noted that both 1- and 2-naphthols undergo this reaction, and that more than one hydrazine residue can be introduced readily.

When phenylhydrazine, sodium bisulfite, and a naphthol (or naphthylamine) are heated together a rather complicated series of reactions takes

²³ Ger. pat., 676,856 [C. A., 33, 7319 (1939)].

Brit. pat., 479,447 [C. A., 32, 5003 (1938)].
 Franzen, Habilitationsschrift, Heidelberg (1904).

^{22 (}a) Franzen, J. pralit. Chem., 76, 205 (1907); (b) 78, 143 (1908); (c) 78, 157 (1908); (d) Ber., 38, 266 (1905).

²⁷ Bucherer and Schmidt, J. prakt. Chem., [2] 79, 369 (1909).

place. The process has been carefully studied by Fuchs and Niszel.23 who have presented the mechanism shown below.

Bucherer and co-workers 29, 30 investigated the reaction earlier but concluded that products corresponding to V were probably carbazole-Xsulfonic acids because of the ease with which they lost the sulfonic acid residues and yielded carbazoles. These investigators also noted the formation of diamines (corresponding to IV) as by-products. Fuchs' proof that the transformations I → VII → VIII → IX → VI can actually be carried out 33 makes the reaction of naphthols or 2-hydroxy-3naphthoic acid with phenylhydrazine and bisulfite, and that of naphthylhydrazines with bisulfite, quite understandable. Thus phenythydrazine and 2-hydroxy-3-naphthoic acid react to give a 70% yield of a compound of type V which is readily cleaved by acid with the formation of 5,6benzocarbazole." If 2-naphthol is substituted for hydroxynaphthoic acid, the reaction takes place much more sluggishly and the yield of carbazole is only 46% after several days at 130° r p-Tolylhydrazine yields similar products.27

²⁰ Fuchs and Nissel, Ber., 60, 209 (1927).

Bucherer and Seyde, J. prakt Chem., [2] 77, 493 (1908). W Bucherer and Sonnenberg, J. pralt. Chem, [2] 81, 1 (1910).

ring containing the free aromatically bound amino or hydroxyl group (directed coupling). For example, diazonium salts might couple with 1,8-dihydroxynaphthalene-4-sulfonic acid in either the 2- or the 7-position. Actually the first mole of diazo compound couples almost exclusively in the 2-position. When sodium bisulfite reacts with 1,8-dihydroxynaphthalene-4-sulfonic acid, the ring holding the sulfonic acid group is involved (activating influence of the 4-sulfonic acid). The reaction product couples with a diazo compound to form a substance of the following structure.

When this compound is warmed with alkali, it is reconverted to a dihydroxynaphthalenesulfonic acid.

Thus a directed coupling has been accomplished. This azo compound could be again coupled with a different diazonium salt with formation of a bis-azo dye.¹²

Suitably located amino groups can be diazotized more cleanly in addition compounds because the hydroxyl-containing rings are considerably less reactive toward chance excess of nitrous acid than those of the parent aminonaphthols.¹² Azo dyes related to a naphthol can be made sufficiently water-soluble as addition compounds with bisulfite, even though they contain originally no sulfonic acid group, so that they can be applied to the fiber. The combined bisulfite can be removed when the dye is on the fiber.¹²

SELECTION OF EXPERIMENTAL CONDITIONS

Experimental conditions necessarily vary over a wide range. Reaction may take place at a temperature as low as 90°, or it may proceed

satisfactorily only in the neighborhood of 150°. If some of the reactants are only sparingly soluble, intimate mixing of the phases is essential to the success of the process. Aminations involving the use of ammonia and ammonium sulfite are ordinarily conducted in closed vessels at temperatures from 100–150°. Arylaminations will proceed slowly under reflux but take place more rapidly in an autoclave at about 150°. General directions for preparation of N-aryl-2-naphthylamine derivatives are given by Bucherer. In The requisite 2-naphthylamine derivatives are given by Bucherer. In the requisite 2-naphthylamine sulfonic acid is dissolved in a minimum of boiling water and then gradually mixed at 80–90° with a warm solution of sodium hisulfite. If a sulfonic acid should be satted out by the mixing, the salt is brought back into solution by warming on the water bath. The aromatic amine is next added either as such or as a mixture of the hydrochloride and an equivalent of aqueous sodium hydrovide.

The mixture is then heated under reflux until a titration with p-nitrobenzenediazonium ehloride shows no more decrease in original naphthol and no increase in product. To carry out the test for complete reaction a small test portion of the mixture is made distinctly alkaline to phenolphthalein and freed of the excess of the amine used as aminating agent by steam distillation. The mixture is then made acid to Congo red with sulfuric acid and boiled until all the sulfur diexide has been expelled. Diazonium salt solution is then added dropwise from a calibrated pipet until a drop of the mixture on filter paper shows no color in the run-out either with the diagonium salt solution or with Schaeffer's acid (2-hydroxynaphthalene-6-sulfonie acid) As soon as this point is reached. the precipitated dye is filtered from the main test portion and washed with a little saturated sodium chloride solution, the mashines being added to the test portion. Sodium acetate is then added to the test solution, and the solution is again titrated with the same diazonium salt solution. The ratio of the volume of diazonum salt solution employed in the coupling in acid solution and the volume used in the coupling in sodium acctate solution gives the proportion between the newly formed amine and the remaining naphthol

If specific directions for the preparation of the desired compound are not available, orientation experiments controlled as above, using relatively small quantities of material, are necessary in order to determine optimum conditions of time, temperature, and proportions of reactants.

The following examples illustrate both simple amination and aryl amination.

When a naphthylhydrazine reacts with aqueous bisulfite the first reaction apparently is removal of the hydrazine residue with the formation of the bisulfite addition compound of the parent naphthol ²⁷ which then combines with unchanged naphthylhydrazine to form a compound similar to III. If 1-naphthylhydrazine is used, this product is apparently stable ²⁷ but is converted by treatment with hot mineral acids into 1.2.7.8-dibenzocarbazole.

2-Naphthylhydrazine behaves somewhat differently in that the principal products are 3,4,5,6-dibenzocarbazole and a compound of type V. This substance loses its sulfonic acid group readily to form the corresponding carbazole. Experiments ²⁷ have shown that it is possible to prepare the type V compound from 2-hydroxynaphthoic acid directly by treatment with 2-naphthylhydrazine in sodium bisulfite solution. 1-Naphthylhydrazine also condenses easily with 2-hydroxy-3-naphthoic acid; the condensation product (type V) is formed in good yield and is readily transformed into 1,2,5,6-dibenzocarbazole by the action of mineral acid.²⁷

1-Naphthylamine-1-sulfonic acid and the corresponding naphtholsulfonic acid react readily with phenylhydrazine in the presence of bisulfite. Apparently the reaction proceeds to a type III compound; evidence for the structure of this compound is its conversion by oxidation in alkaline solution into 1-phenylazonaphthalene-1-sulfonic acid. Treatment with hot concentrated hydrochloric acid converts the hydrazo compound in part into 1,2-benzocarbazole.²⁰

During the treatment with acid the nuclear sulfonic acid group is cleaved by hydrolysis.

The action of phenylhydrazine and sodium bisulfite on a number of naphthylamine- and naphthol-sulfonic acids has been studied. 10, 11, 12, 11 In all instances the reactions which occur can be interpreted in terms of the mechanism proposed by Fuchs and Niszel. These investigations 10 indicate that reactions which involve compounds of the 1-series and phenylhydrazinc usually proceed only to type II1 compounds (except 1naphthol- and 1-naphthylamine-5-sulfonic acid). The hydrazo compound can be converted by treatment with mineral acid into a carbazole. Reactions which involve members of the 2-series proceed to type V compounds from which the sulfonic acid group is readily cleaved by hydrolysis in mineral acid solution. Numerous examples of carbazoles prepared by this method will be found in the table of compounds prepared by the Bucherer reaction (pp. 124-7).

Reactions involving aminonaphtholsulfonic acids, phenylhydrazine, and bisulfite are complex 20. 21. 23 Azo dyes also react with sodium bisulfite and phenylhydrazine, but here again the reactions are complex

and the nature of the products is obscure.

In general the reaction of a hydrazine with a naphtbol (or naphthylamine) in the presence of bisulfite takes place more readily than the corresponding reaction involving an amine and a naphthol (or naphthylamine). In this connection it is interesting to note that "R acid" (2-naphthol-3,6-disulfonic acid), which does not react with amines 15 in the presence of bisulfite because of the hindering effect of the 3-sulfonic acid. condenses readily with phenyllaydrazine under similar conditions.

The Use of Bisulfite Addition Products in the Preparation of Azo Compounds

Bisulfite addition products obtained from dihydroxy- or diaminonaphthalenes can be employed in the preparation of azo dyes. Those compounds containing a free amino group in the aromatic ring of the addition complex can be converted into diazonium salts which couple in the usual way. After the coupling the hydroxyl group can be regenerated by treatment with alkali or the addition product can be converted into an amine. Obviously a hisulfite addition product can be coupled with any diazonium salt provided that there is an activating group (hydroxyl or amino) in the aromatic ring, coupling must take place in the

n König and Haller, J. prof.t. Chem., 101, 38 (1920). 11 Bucherer and Zimmermann, J. prokt. Chron., 103, 277 (1921).

¹² Bucherer and Wahl, J. prakt. Chem., 103, 253 (1921).

ring containing the free aromatically bound amino or hydroxyl group (directed coupling). For example, diazonium salts might couple with 1,8-dihydroxynaphthalene-4-sulfonic acid in either the 2- or the 7-position. Actually the first mole of diazo compound couples almost exclusively in the 2-position. When sodium bisulfite reacts with 1,8-dihydroxynaphthalene-4-sulfonic acid, the ring holding the sulfonic acid group is involved (activating influence of the 4-sulfonic acid). The reaction product couples with a diazo compound to form a substance of the following structure.

When this compound is warmed with alkali, it is reconverted to a dihydroxynaphthalenesulfonic acid.

Thus a directed coupling has been accomplished. This azo compound could be again coupled with a different diazonium salt with formation of a bis-azo dye.¹²

Suitably located amino groups can be diazotized more cleanly in addition compounds because the hydroxyl-containing rings are considerably less reactive toward chance excess of nitrous acid than those of the parent aminonaphthols.¹² Azo dyes related to a naphthol can be made sufficiently water-soluble as addition compounds with bisulfite, even though they contain originally no sulfonic acid group, so that they can be applied to the fiber. The combined bisulfite can be removed when the dye is on the fiber.¹²

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The mixture is then heated under reflux until a titration with p-nitrobenzenediazonium chloride shows no more decrease in original naphthol and no increase in product. To carry out the test for complete reaction a small test portion of the mixture is made distinctly alkaline to phenolphthalein and freed of the excess of the amine used as ammating agent by steam distillation. The mixture is then made and to Congo red with sulfuric acid and boiled until all the sulfur droude has been expelled. Diazonium salt solution is then added dropwise from a calibrated pipet until a drop of the mixture on filter paper shows no color in the run-out either with the diazonium salt solution or with Schaeffer's acid (2-hydroxynaphthalene-6-sulfonic acid). As soon as this point is reached. the precipitated dye is filtered from the main test portion and nashed with a little saturated sodium chloride solution, the washings being added to the test portion. Sodium acetate is then added to the test solution, and the solution is again tetrated with the same diazonium salt solution. The ratio of the volume of diazonium salt solution employed in the coupling in acid solution and the volume used in the coupling in sodium acetate solution gives the proportion between the newly formed amine and the remaining naphthol.

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The following examples illustrate both simple amination and arylamination

1

EXPERIMENTAL PROCEDURES

Preparation of 2-Naphthylamine

One hundred forty-four grams (1 mole) of 2-naphthol is placed in a suitable pressure vessel together with a solution of ammonium sulfite prepared by passing sulfur dioxide into 400 cc. of cooled, concentrated ammonia (sp. gr. 0.90) until 100 g. of gas has been absorbed. An apparatus such as that employed for high-pressure hydrogenation will serve; it is essential that provision be made for shaking or stirring the reaction mixture. The autoclave is closed and heated at 150° with continual shaking or stirring for eight hours and is then allowed to cool with shaking.

The reaction mixture is removed from the autoclave, which is rinsed with about 500 cc. of water. The product is filtered on a Büchner funnel, and the crude material is dissolved in a boiling mixture of 150 cc. of concentrated hydrochloric acid and 400 cc. of water and then diluted with 1 l. of water. Ten grams of Norit is added, and the mixture is boiled for five minutes. After filtration (heated funnel) from any undissolved dinaphthylamine, the product is precipitated by pouring the hot solution with stirring into a solution of 120 g. of sodium hydroxide in 500 cc. of water. The resulting slurry, which should be alkaline to phenolphthalein, is cooled with stirring to 20°, filtered, and washed with 2 L of cold water.

The product is dried to constant weight at 50°. It is a light tan powder and weighs 135-137 g. (94-96% of the amount theoretically possible). The product melts at 111-112°.

Preparation of 7-Methyl-1-naphthylamine 24. 25

A mixture of 50 g. of 7-methyl-1-naphthol, 150 cc. of water, 75 cc. of freshly prepared ammonium sulfite solution (prepared from aqueous ammonia [sp.gr. 0.90] and sulfur dioxide), and 75 cc. of aqueous ammonia solution (sp.gr. 0.90) is prepared in a 35-mm. Pyrex tube approximately 400 mm. in length. The tube is carefully sealed and heated in an electrically heated furnace constructed of iron pipe and attached to a shaking machine.

The furnace is heated to a temperature of 160–165° as recorded by a thermometer under the resistance wire, and the furnace and its contents are shaken at this temperature for thirty to thirty-five hours. The shaker is then stopped and the furnace allowed to cool to room temperature before it is opened.

²⁴ Ruzicks and Morgeli, Hele. Chim. Acta, 19, 377 (1936).

²⁵ Howard, Ph.D. thesis, University of Maryland, p. 25 (1938).

The contents of the tube are extracted with three 250-ce, portions of ether; the extracts are combined and extracted with 1076 hydrochloric acid until a small test portion of the last extract gives no precipitate of amine when made alkaline with 1076 aqueous sodium hydroxide. The extracts are made alkaline with 1076 aqueous sodium hydroxide, whereupon the amine precipitates and is filtered and dried in vacuum. The yield is 40-45 g. (80-2075). The combined yields of several such runs are distilled from a sausage flask under 3 mm, pressure. The bulk of the material boils at 130-14073 mm.; the product melts at 58-59°. If desired the amine can be crystallized from petroleum ether, from which it separates in the form of fine needles.

Preparation of 2-p-Tolylamino-5-hydroxynaphthalene-7-sulfonic Acid

A mixture of 216 g. (2 moles) of distilled p-tolaidine, 215 g (0.9 mole) of 2-amino-5-hydroxynaphthalene-7-sulfonic acid ("J acid"), 167 g. of sodium bisulfite, and 500 cc. of water, in a 3-L three-necked round-bottomed flask provided with a reflux condenser and a mechanical stirrer, is heated under reflux with stirring for thirty hours. Sodium carbonate is then added until the mixture is alkaline and the excess p-toluidine is removed by steam distillation. The residual solution is cooled in a refrigerator until crystallization is complete, and the crystals are sucked dry on a Büdiner funnel and washed with about 50 cc. of cold saturated sodium chloride solution. The product is dissolved in about 700 cc. of hot water to which enough hydrochloric acid is added to make the mixture acid to Congo red. The mixture is allowed to stand in a refrigerator until crystallization is complete; the crystalline acid is filtered and washed on the filter with a little ice-cold hydrochloric acid and then twice with small portions of cold water. The 2-p-tolylamino-5-hydroxy-T-sulfonic acid is dried at 100°; it weighs about 185 g (65%).

Preparation of 2-(4'-Hydroxyphenylamino)-8-naphthol-6-sulfonic Acid and 2-(4'-Hydroxyphenylamino)-naphthalene-6-sulfonic Acid n

A mixture of 25 g, of "\gamma acid" (2-amino-8-hydroxynaphthalene-6-sulfonic acid), 50 cc. of water, 250 g of solium bisulfite solution (33%), 20 g, of p-aminophenol hydrochloride, and 16 g of sodium hydrodied is boiled under reflux for twesty hours. When the mixture has cooled to room temperature, it is acidified to Congo paper and the crude product is filtered on a Bulchner funnel. It is purified by solution in alkala and preprecipitation by acid. The pure product weighs about 13 g, (37 8%).

Substitution of 25 g. of "Scharffer's arid" (2-hydroxynaphthalene-fulfonic acid) for "y acid" above results in a yield of 20 g. (61%) of 2-(4'-hydroxynhenylanino)-naphthalene-6-sulfonic acid.

COMPOUNDS PREPARED BY THE BUCHERER REACTION

(Types of reaction are referred to by numbers as follows.)

I. ArOH

 $\rightarrow ArNH_2$

II. $ArNH_2$

→ ArOH III. ArOH or ArNH2 - ArNHR or ArNR2

IV. ArOH or ArNH₂ → ArNHAr'

V. ArOH or ArNH₂ → ArNHNH₂

VL ArOH or ArNH2 → A carbazole

				,
Formula	Name of Compound	Type	Yield,	Reier- ence *
C ₅ H ₆ O ₂	Resorcinol	11		51
C.H.ON	m-Aminophenol	I		48
CeHeN2	m-Phenylenediamine	I	\$0	3, 4S
C6H10N4	1,3-Phenylenedihydrazine	7	20, 75	22a, 26c
C7H5O2	2,4-Dihydroxytoluene	П	_	51
C ₂ H ₂ N ₂	6-Aminoquinoline	I	_	14
$C_2H_3N_2$	S-Aminoquinoline	I	Almost	14
	1		quant.	
$C_9H_9O_2NS$	8-Aminoquinoline-5-sulfonic acid	1		14
$C_{12}H_{2}N$	2-Naphthylamine	I I	67, S7-SS	2, 3, 15,
23 .			l .	16,35,37,
			}	± S
$C_{10}H_{10}N_2$	1,5-Diaminonaphthalene	1	<u> </u>	4S
$C_{16}H_{16}N_2$	2,7-Diaminonaphthalene	I	69	3
$C_{10}H_{10}N_2$	1-Naphthylhydrazine	7.		26d
C13H12N4	2,3-Naphthylenedihydrazine	7	57	264
$C_{12}H_{5}O_{4}S$	1-Naphthol-1-sulfonic acid	Π	Quant.	1, 2, 3,
				12, 38, 39
$C_{10}H_{\xi}O_{\xi}S$	1-Naphthol-6-sulfonic acid	П		39
$C_{13}H_5O_4S$	1-Naphthol-7-sulfonic acid	11	_	2, 12
C_1 : H_5O_4 S	1-Naphthol-S-sulfonic acid	II	_	12
C_1 U H_5 O $_4$ S	2-Naphthol-6-sulfonic acid	Π	_	51, 53
$C_{15}H_{5}O_{4}S$	2-Naphthol-S-sulfonic acid	П	<u> </u>	53
$C_{13}H_5O_5S$	1,5-Dihydroxynaphthalene-1-sulfonic acid	\mathbf{II}	-	40
C_1 : H_5O_5S	1,5-Dihydroxynaphthalene-7-sulfonic acid		<u> </u>	32, 40
C_1,H_2O_2S	1,8-Dihydroxynaphthalene-1-sulfonic acid		_	2, 39
C_1 : H_1O_1 S	1.8-Dihydroxynaphthalene-5-sulfonic acid		<u> </u>	2
$\mathbf{C}_{\mathtt{I} \cap} \mathbf{H}_{\mathtt{S}} \mathbf{O}_{\mathtt{S}} \mathbf{S}$	2.5-Dihydroxynaphthalene-1-sulionic acid		· —	33
$C_1:H_5O_5S$	2.5-Dihydroxynaphthalene-7-sulionic acid		90	3, 51, 53
$C_{10}H_4O_7S_2$	1-Naphthol-4,6-disulfonic acid	П	· -	12
C_1 ; $H_5O_7S_2$	1-Naphthol-1,7-disulfonic acid	II	; —	12
$C_{10}H_5O_7S_2$	1-Naphthol-4,8-disulfonic acid	II	Quant	3, 12
	4	,	•	

^{*} References 25 to 55 appear on p. 128.

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Formula	Name of Compound	Type	Tield,	Refer-
CtoHsOrSa	1-Naphthol-6,8-disulfonic acid	II	_	12
C10H5OsS2	1,8-Dihydroxynaphthalene-1,6-disulfonic		1 -	12
	acid	n	l –	32
$C_{10}II_{5}O_{10}S_{2}$	1-Naphthol-4,6,8-trisulfonic acid	111	_	12
CloIlaON	1-Amino-2-naphtbol	I		84
C10H2ON	I-Amino-1-naphthol	1	35	84
CatllaON	1-Amino-5-naphthol	II I	80	3
C10II10N	I-Amino-8-naphthol	II		12
CioII ON	2-Amino-7-naphthol	п		53
C10H10ON2	7-Hydroxy-2-naphthylhydrazine	v	82	266
CtoH OaNS	I-Naphthylamine-t-sulfonic acid	i	-	48
CtoH ₀ O ₂ NS	2-Naphthylamine-1-sulfonic acid	i	_	12
C10II 0 NS	2-Naphthylamine-6-sulfonic acid	i	_	12, 22
CiaHoOaNS	2-Naphthylamine-7-sulfonic acid	lî.		12
CtcHoO1NS	2-Naphthylamine-8-sulfonic acid	Î	_	22
CloHONS	1-Amino-5-naphthol-2-sulfonic acid	l ù l	-	40
CiellaO.NS	I-Amino-5-naphthol-4-sulfonic acad	11,1	_	40
CicHoO, NS	I-Amino-5-naphthol-7-sulfonic acid	1	_	48
CiellaOaNS	I-Amino-5-naphthol-S-sulfonic acid	n l		40
CtoHoO.NS	1-Amino-7-naphthol-1-sulfonic acid	ï		23
CicHoOANS	1-Amino-8-naphthol-5-sulfonic acrd	n l		12, 39, 49
C10H0O4NS	2-Amino-5-naphthol-7-sulfonic acid	ï		3
C10II.O.NS	2-Amino-S-naphthol-G-sulfonic acid	î	80, 59	3, 13
C10H4O4NS	2-Naphthylamme-6,8-disullonic acid	î	00,00	12
C10H10O1N1S	1.5-Diammonaphthalene-1-sulfonic acid	î l	- 1	40
CigH10O2N2S	2.5-Diaminonaphthalene-1-sulfonic acid	î l	Quant.	33
CulluOaNS	1-Methylaminonaphthalene-1-gulfonic	٠ ا	Quadr.	Ų.
	newl	111		12, 50
CullinOaNS	2-Methylaminonaphthalene-6-sulfonic	***		10, 00
	acid	m	-	50
CollinOaNS	2-Amino-1-naphthylmethane sulfonic acid	1		52
CullinOaNS	1-Methylammo-7-naphthol-4-sulfonic acid	m		23
CulluNa	1-(\$ Aminoethylammo)-naphthalene	m	1	17
CpH12ONs	3-Hydroxy-1'-aminodiphenylamine	IV	- 1	41
CpH ₁₃ ON	2-(8-Hydroxyethylamino)-naphthalene	III		56
C121112O2N	1-(6-Hydrovyethylamino)-5-naphthol	III	- 1	18
Ci2Hi9ON	2-Hexyl-5-ammophenol	1	70-80	42
C121113O4NS	2-(β-Hydrovyethylamino)-naphthalena-			
	7-sulfonie seid	III	/	56
Chillio NS	1-(β-llydroxyethylammo)-naphthaleas-			
	4-sulfome acid	III		56

^{*} References 36 to 53 appear on p 128

[†] See p 122

COMPOUNDS PREPARED BY THE BUCHERIE REACTION—Continued

Formula Name of Compound Type † Yield	Refer-
C ₁₂ H ₁₂ O ₂ NS 2-(S-Hydroxyethylamino)-S-hydroxy- naphthalene-6-sulfonic acid III —	56
C12H1:O2N2S I-(S-Aminoethylamino)-naphthalene-i-sulfonic acid III -	19
C ₁₇ H ₁₄ O ₂ N ₂ 2-(2-Aminoethylamino)-naphthalene-6- carboxylic acid III —	57
C ₁₂ H ₁₂ ON 2-(Methyl-3-hydroxyethylamino)- naphthalene-6-sulfonic acid III —	56
C ₁₂ H ₁₅ O ₅ NS 2-(\$\sigma \text{Hydroxyethylamino} - \sigma \text{methoxy-} \ \text{naphthalene-6-sulfonic acid} \text{III} -	56
C ₁₆ H ₁₅ N ₂ 2-(c-Aminobutylamino)-naphthalene III — C ₁₆ H ₁₅ N ₃ 2-(c-Aminoethylaminoethylamino)-	17
naphthalene III — C14H2:O2Ne 1,5-Bis(S-hydroxyethylamino)-	17
raphthalene III — C1:H1:ON 1-(4'-Hydroxyphenylamino)-naphthalene IV —	1S 43
C15H11O2N2 2-(\(\alpha\)-Aminobutylamino)-naphthalene-6- carboxylic acid III —	57
C ₁₂ H ₁₁ N Benzo-(1,2)-carbazole VI 75 C ₁₂ H ₁₁ N Benzo-(3,4)-carbazole VI 46	29, 30 28, 29, 30
C::HuN Benzo-(5,6)-carbazole VI — C::HuN 2-Phenylaminonsphthalene IV 65	32 21, 24, 44
C ₁ (H ₁₄ N ₂ 2-(4'-Aminophenylamino)-naphthalene IV 64 C ₁ (H ₁₁ ON 1-Hydroxybenzo-(3.4)-carbazele VI —	13 28
C::H::ON 4'-Hydroxybenzo-(3.4.1',2')-carbazole VI 69 C::H::ON 1'-Hydroxybenzo-(3.4.2',3')-carbazole VI —	2S 33
C ₁₆ H ₁₇ ON 1-Phenylamino-4-nephthol IV — C ₁₆ H ₁₇ ON 1-Phenylamino-5-nephthol IV 96	43 22a, 43
C ₁₇ H ₁₇ ON 2-Phenylamino-5-naphthol IV 70 C ₁₇ H ₁₇ ON 1-(4'-Hydroxyphenylamino)-naphthalene IV —	22z. 33 24. 45
C ₁ :H ₁ :ON 2-(4'-Hydroxyphenylamino)-naphthalene IV 7- C ₁ :H ₁ :O ₂ N 2-(4'-Hydroxyphenylamino)-7-naphthol IV	21 24
C ₁₁ H ₁₁ O ₁ NS Benzo-(1.2)-carizazole-3-sulionic acid VI — C ₁₁ H ₁₁ O ₁ NS Benzo-(1.2.1'.2')-carizazole-1'-sulionic acid VI —	27 30
C ₁₁ H ₁₁ O ₁ NS Benzo-(1.2.1'2')-earbarole-5'-culfenic acid VI — C ₁₁ H ₁₂ O ₁ NS Benzo-(3.4.1'2')-earbarole-5'-culfenic acid VI —	32 30
C::H::O4NS 3'-Hydroxybenzo-(1.2.1',2')-corbozo!e-5'- sulfonic acid VI —	32
CnHnO.NS 1'-Hydroxybenzo-{3,4,2',3'}-carbazole-5'- sulfenie acid VI —	32

^{*} Reference 35 to 35 appear on p. 128. † See p. 122.

		1		
Formula	Name of Compound	Type †	Yield,	Refer- ence
CitlinO4NS	5'-Hydroxybenzo-(3,4,3',4')-carbazole-I'-		-	
	sulfonic acid	VI		32
C16H11O4NS2				
	acid	VI	-	30
C161133O3NS	2-Phenylaminonaphthalene-6-sulfonic	[]		[
	neid	IV		11,21,22
		- 1		58
C16I113O3NS	2-Phenylaminonaphthalene-8-sulfonie			l
G 11 0 MG	acid	IV	34	21, 22
C14113O2NS	2-Phenylaminonaphthalene-3'-sulfone	IV		
C14H13O4NS	2-(4'-Hydroxyphenylamino)-naphthalene-	14		13
Chillotte	6-culfonic acid	Iv [ĺ
C1sH1sO4NS	2-(4'-Ilydroxyphenylamino)-naphthalene-	117		21
Olithottes	8-sulfonic acid	Iv	98	21
C18H12O4NS	2-Phenylamino-5-paphthol-7-sulfonic acid	iv	ขอ	21
Cie II 11O4NS	2-Phenylamino-8-naphthol-6-sulfonic acrd	iv	80	21
C16H11O6NS	2-(4'-Hydroxyphenylamino)-8-naphthol-	٠, ا		
Office Paris	6-sulfonic acid	īv		21
CasHasOaNSa	2-Phenylaminonaphthalene-6.4'-disul-			
	fonic scid	ıv	83	21
CleHisOaNS:	2-Phenylaminonaphthalene-6,3'-disul-			
	fonic acid	IV	89	21
C15II12O6NS2	2-Phenylaminonaphthalene-5,7-disulfonie	- 1	- 1	
	acid	IV)	2
$C_{16}II_{12}O_6NS_2$	2-Phenylaminonaphthalene-6,8-disulfonic		1	
_	acid	IV		2
C16H13O7NS1	2-(4'-Hydroxyphenylammo)-naphthalene-			
	6,8-disulfonic neid	IV	84	13
C16H14O3N2S	I-(4' Aminophenylamino)-naphthalene-	IV		41
C16H4O2N2S	4-sulfonic acid 2-(4'-Ammophenylamino)-naphthalene-	AV	_	41
C161114O31499	6-sulfonic acid	IV	72	21
$C_{18}H_{14}O_{4}N_{2}S_{2}$				
C161114O614202	6.8-disulfone seid	IV	82	13
C17H15N	6-Methylbengo-(3.4)-carbasole	VI		29
C ₁₂ 11 ₁₈ N	2-v-Tolylaminonaphthalene	IV	82	13
C ₁₇ H ₁₅ N	2-(3'-Methylphenylammo)-naphthalene	IV	34	13
C ₁₇ H ₁₈ N	2-(2'-Methylphenylamino)-naphthalene	IA	28	13
C17H16N2	2-(3'-Amino-4'-methylphenylamino)-			
	naphthalene	IV	55	13

References 36 to 58 appear on p 125.
 See p. 122.

^{, , . .}

COMPOUNDS PREPARED BY THE BUCHERER REACTION-Continued

		1	i	1
Formula	Name of Compound	Type †	Yield,	Refer- ence *
CpHnON	4'-Methoxybenzo-(3,4,1',2')-carbazole	VI		28
C ₁₇ H ₁₅ O ₂ N	2-(2'-Carboxyphenylamino)-naphthalene	IV	17	13
C ₁₇ H ₁₂ O ₂ N	2-(3'-Carboxy-1'-hydroxyphenylamino)-	1	••	1 ~
01:11120314	naphthalene	IV		13
C17H15ON	1-(4'-Methoxyphenylamino)-naphthalene	IV		24, 45
C ₁₇ H ₁₅ ON	2-(4'-Methoxyphenylamino)-naphthalene	iv	74	13
C ₁₇ H ₁₅ ON	2-(2'-Methoxyphenylamino)-naphthalene	IV.	27	13
C ₁₇ H ₁₃ O ₄ NS	1-(4'-Hydroxy-3'-carboxyphenylamino)-	1 '	~,	
C171113O8.N3	naphthalene-1-ulfonic acid	IV.		47
C17111106NS	2-(4'-Hydroxy-3'-carboxyphenylamino)-			
	naphthalene-7-sulfonic acid	IV		46, 47
C17H13O6NS	2-(4'-Hydroxy-3'-carboxyphenylamino)-			
	naphthalene-6-sulfonic acid	IV		47
C1:11120°ZZ	2-(4'-Hydroxy-3'-carboxyphenylamino)-			457
	naphthalene-S-ulfonic acid	IV	_	47
C17H13O7NS	2-(4'-Hydroxy-3'-carboxyphenylamino)-			
	S-naphthol-6-sulfonic acid	IV		47
$C_{17}H_{12}O_{2}NS_{2}$	1-(4'-Hydroxy-3'-carboxyphenylamino)-	71.		
0. 27. 0.270	naplithalene-3,8-disulfonie acid	IV	-	47
C ₁₇ H ₁₃ O ₉ NS ₂	1-(4'-Hydroxy-3'-carboxyphenylamino)-		- 1	
0.77.0.370	naphthalene-6,8-disulfonic acid	IV		47
$C_{17}H_{15}O_{2}NS$	2-o-Tolylaminonaphthalene-6-sulfonic	IV	51	21
C ₁₇ H ₁₅ O ₃ NS	2-p-Tolylaminonaphthalene-6-sulfonic	*	01	~-
01/11/503112	acid	IV	35	21
C17H15O2NS	2-p-Tolylaminonaphthalene-8-sulfonic	1 1	00	~-
01,111,00,110	acid	IV	Pract.	
,			quant.,	
			76	11, 21
$C_{17}H_{15}O_4NS$	2-p-Tolylamino-8-naphthol-6-sulfonic	1		,
	acid	IV.	_	13
C17H15O5NS2	2-p-Tolylaminonaphthalene-6,8-disulfonic			
	acid	IA	- 1	21
$C_{15}H_{16}N_2$	N-N-Diphenyl-m-phenylcnediamine	IV	_	43
$C_{15}H_{17}N$	2-(2',4'-Dimethylphenylamino)-naphtha-	- 1		
	lene	IV	-	13
$C_{15}H_{13}O_5N$	8-Phenylamino-2-naphthol-3,2'-dicar-			
A =	boxylic acid	IV	-	43
$C_{18}H_{15}O_4N$	8-(4'-Methoxyphenylamino)-2-naphthol-		1	
	3-carboxylic acid	IV	-	43

^{*} References 36 to 55 appear on p. 128.

[†] See p. 122.

COMPOUNDS PREPARED BY THE BUCHERER REACTION-Continued

Formula	Name of Compound	Type †	Yield,	Refer-
C18H17ON	2-(4'-Ethoxyphenylamino)-naphthalene	IV	61	13
$C_{15}II_{17}O_3NS$	2-(2',4'-Dimethylphenylammo)-naphtha-	, ,		
	lene-6-sulfonic acid	IV	58	21
C13H17O4NS	2-p-Ethoxyphenylaminonaphthalene-6-	1 1		1
C T O NO	sulfonic acid	IV	69	21
C19H17O4N8	2-p-Ethoxyphenylaminonaphthalene-8- sulfonic acid			
CIMITO NS	2-p-Ethoxyphenylamine-8-naphthol-6-	IV	50	21
Claritorias	sulfonie acid	11.		
CmH12N	Dibenzo-(3,4,5,6)-carbazole	VI	86	21
C201131N	Dibenzo-(1,2,7,8)-carbazole	VI	- 1	27 27
CmH:sON	1-(2'-Naphthylamino)-7-naphthol	IV		43
ConHisON	8-(2'-Naphthylamno)-2-naphthol	VI	84	220
CaoHisoN	1-(4'-Hydrotyphenylamino)-anthracene	iv	82	22a
Callino, NS	2,2'-Dinaphthylamine-6,6'-disulfonic acid	iv	02	11
C22 H14 N2	Carbagolo-(3.4,3',4')-carbagole	VI	- 1	29
CapH14OaNa	2,7-Di(4'-hydro typhenylamino)-naphtha-	- 1		20
C2211102117	lene	IV	- 1	45
C22H15O4N2S		**		40
-11-x12-4-150	benzidine	IV	- 1	54. 55
CulfusQaNaS	N-(8"-Hydroxy-6"-sulfo-2"-naphthyt)-		- 1	,
-11-110-04-1-0	beneidioe	77	- 1	54
C+HeO-NoSa	N.(5"-Hydroxy-7"-sulfo-2"-naphthyl)-		- 1	
	benzidine-3'-sulfonie acid	IV	- 1	51.55
CarHaO: NaSa		1	1	.,
	benzidine-3'-sulfonic acid	IV	- 1	51
Callado,NaS	N-(5"-Hydroxy-7"-culfo-2"-naphthyl)-			
	tolidine	IV	-	55
C24H22O5N2S	N-(5"H) droxy-7"-sulfo-2"-naphthyl)-	- 1	1	
	dianisidate	IV		55
C24H22O7N2S2		- 1	- 1	
1	tolidine-3'-sulfonic acid	IV	- 1	55
C28II22O2N2S	N-(2-Naphthyl-6-sulfo)-p-rosaniline	IV	- [21
C32H24O2N2	N,N'-Bis(5"-hydroxy-1"-naphthyl)-	- 1	(
- (benzidme	W	- 1	43
CaHnO7NS	Dibenzoate of dinaphthocarbazole from	***	1	
1	"J acid"	VI	- 1	31

^{*} References 35 to 53 appear on p. 128.

[†] See p 123

- 25 Levi, Giorn. chim. ind. applicata, 3, 97 (1921).
- F Brit. pat., 184,284 [C. A., 17, 110 (1923)].
- 25 U. S. pat., 1.880,701 [C. A., 27, 515 (1933)].
- ²³ Ger. pat., 109,102 [Frdl. 5, 164 (1897-1900)].
- 45 Bucherer and Uhlmann, J. prakt. Chem., [2] 80, 201 (1909).
- 42 Ger. pat., 451.980 [C. A., 22, 4130 (1928)].
- 4 Hartung, Minnick, and Koehler, J. Am. Chem. Soc., 63, 507 (1941).
- Ger. pat., 643,221 [C. A., 31, 4342 (1937)]; Brit. pat., 451,348 [C. A., 31, 113 (1937)].
- "Fr. pat., 750,243 [C. A., 28, 779 (1934)].
- 45 Fr. pat., 807,765 [C. A., 31, 5813 (1937)]; cf. Fr. pat., 645,150, and Ger. pat., 642,549.
- "Fr. pat., 789,589 [C. A., 30, 2019 (1935)].
- 47 Brit. pat., 437,798 [C. A., 30, 2203 (1935)].
- 45 Ger. pat., 117,471 [Frdl., 6, 190 (1900-02)].
- 43 Ger. pat., 120,016 [Chem. Zentr., I, 1074 (1901)].
- E Ger. pat., 121,683 [Frdl., 6, 192 (1900-02)].
- ²¹ Ger. pat., 126,136 [Frdl., 6, 189 (1900-02)].
- E Ger. pat., 132,431 [Frdl., 6, 193 (1900-02)].
- 57 Ger. pat., 134,401 [Frdl., 6, 185 (1900-02)].
- H Ger. pat., 254,510 [C. A., 7, 1617 (1913.].
- 35 Brit. pat., 11,427 [C. A., 6, 3023 (1912)]. M Ger. pat. 442,310 [Frdl., 15, 511 (1927-29)].
- "U. S. pat. 1,727,595 [cf. Ger. pat., 468,811 (C. A., 23, 2723 [1929]); Frdl., 16, 510 (1927-29)].
 - 51 Ger. pat., 122,570 [Frdl., 6, 194 (1909-02)].

General Reference, Bucherer Reaction

BUCHERER, "Lehrbuch der Farbenchemie," 2nd ed., p. 200, Otto Spamer, Leipzig 1914.

CHAPTER 6

THE FIRS REACTION

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MYTTYM

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INTRODUCTION

Diard Letones Laxing a methol or metholene substituent adjacent to the cathenal group often suffer cyclodelaydration when submitted to pyrolises and afford a certain anyont of the corresponding anti-parent derivative. Although an early instance of the products in of a hydro-

carbon by the process was regested by "the left and each begin the

" Bake and you have & r. d. 221 alors | E. es. 18"4 129

reaction is generally accredited to Elbs,2 for this investigator was the first to explore the generality and synthetic uses of the reaction. Elbs and his co-workers studied the pyrolysis of various polyalkylbenzophenones and, finding that some of these substances failed to condense while others afforded anthracene homologs in no better than 20-25% vield (Table 1), were inclined to discount the value of the method, particularly where the hydrocarbon in question can be obtained by the phthalic anhydride synthesis of the anthragminone, followed by reduction. From the accumulated data now available, it has become apparent that, although the Elbs condensation in general is subject to many limitations and shortcomings, there are instances in which the reaction procceds smoothly and affords the best known means of obtaining important hydrocarbons. The reaction also has found significant use in the synthetic preparation of hydrocarbons not available by other known methods. A low yield in the pyrolysis is often offset by the ready availability of the required ketone.

The reaction usually is carried out by heating the ketone without catalyst or solvent at the reflux temperature, or at a temperature in the range 400-150°, until water is no longer evolved. At the high temperature required to effect ring closure considerable carbonization may occur and much material may be lost as the result of cleavage of the ketone by the water liberated, elimination or degradation of alkyl substituents, and molecular rearrangements. The main hydrocarbon reaction product may not be that normally expected on the basis of the structure of the starting material, and the product is frequently, if not always, accompanied by related hydrocarbons. With the exception of a few particularly favorable applications of the reaction, a product of the Elbs condensation usually requires extensive purification, and the probable structure as inferred from analogy should be investigated by independent methods. The total weight of the crude hydrocarbon fraction obtained from the pyrolysis mixture by distillation and initial crystallization usually does not provide a reliable index of the true yield unless the melting point can be shown to be reasonably close to that of a single, fully purified product.

The mechanism of the condensation is not known. Cook 2 suggested

² Elbs and Larsen, Ber., 17, 2847 (1884).

² Claus and Elbs, Ber., 18, 1797 (1885).

Elbs and Olberg, Ber., 19, 408 (1886).

⁵ Elbs, J. prakt. Chem., 33, 180 (1886). ⁶ Elbs, J. prakt. Chem., 35, 465 (1887).

⁷ Elbs, J. prakt. Chem., 41, 1 (1890).

⁵ Elbs, J. prakt. Chem., 41, 121 (1890).

⁹ Cook, J. Chem. Soc., 487 (1931).

that the ketone may undergo tautomerism to an enolic form having a diene system to which intramolecular addition of the attached aryl group may occur, giving the dihydroanthranol. Fieser and Dietz 10

suggested that the same intermediate, which at the pyrolysis temperature certainly would undergo rapid dehydration to the hydroenton, may result alternately from a forced 1,4-addition of the methyl substituent to the conjugated system comprising the carbonyl group and the aryl nucleus. There is no evidence bearing on either hypothesis, and a suggested analogy ii to the formation of anthracene derivatives by the cyclization of o-benzylbenzidehyde ii and o-benzyl diaryl ketones ii does not appear applicable because these cyclizations proceed under the influence of an acid catalyst and at a low temperature and hence under conditions wholly unlike those required for the non-catalytic hightemperature pyrolysis.

EXAMPLES OF THE PEACTION

Synthesis of Anthracene Homologs. Observations concerning the pyrolysis of mono-, dl. tri, tetra, and penta-methyl derivatives of benzophenone are included in Table I. In most instances the material pyrolyzed was the total distilled product of the condensation of a hydrocarbon with an acid chloride or with phospene, and the published data on the pyrolysis temperatures and the yields are not very specific. Seer and co-workers in "followed Ellis" practice of refluxing the ketone gently for a prolonged period but obtained only very low yields. Morgan and Coulson in "found it expedient to shorten the time of reaction and to remove the hydrocarbon formed from time to time in order to protect it from destruction. Although this technique apparently represented a marked improvement, the yields reported refer merely to materials of unspecified until and consequently are ambiguous. The data

¹⁰ Fieser and Diets, Ber., 62, 1827 (1929).

¹¹ E. Bergmann, J. Org. Chem., 4, 1 (1939).

¹¹ Bradsher, J. Am. Chem. Soc., 61, 486, 1077 (1940).

¹³ Seer and Stanks, Monatch., 32, 143 (1911)

¹⁴ Seer and Ehrenzweig. Monath., 33, 33 (1912).

¹⁵ Morgan and Coulson, J. Chem. Soc . 2203 (1929).

¹⁶ Morgan and Coulson, J. Chem. Soc., 2551 (1929).

(42.4.Tetramethyl 2C,II.(CII.)3 + C (5.2.5.Tetramethyl 2C,II.(CII.)3 + C (4,6,3.5.Fentamethyl Aril + Ar COCI	OCI; (70-80%)	6 hr. (b.p. 327°) 6 days 7.5 hr.	1,3,6-Trimethyl 1,4,6-Trimethyl 1,3,5,7-Tetramethyl (as qui- none) 1,Phenyl	20-25 3	4, 6 17
2-Methyl-2'-phenyl	Arcoci + Armer (4576)	RELATED EXAMPLES			
Ketone	Preparation	Pyrolysis	Product	Yield, % ence	Refer- ence
Di-(4-bydrindyl) keton	Di-(4-hydrindyl) ketone ArLi + Ar'CN (51%)	415-420*, 30 min. 420-430*, 2 hr.	1,2-Cyclopenteno-5,10- 21 aceanthrene 1,2-Dimethyl-5,10-acean- 1.3 and 3	21 1.3 and 3	18
+(2',3'-Dimetnylben- royl)-hydrindene			threne and 1-methyl-5,6- cyclopentenoanthracene		
11 Cook, J. Chem. Soc., 1087 (1930).	11 Cook, J. Ohem. See , 1087 (1930). 11 Finer and Herabberg, J. Am. Chem. Soc., 89, 304 (1937).				

for the series of homologs hardly warrant any general conclusion except that some o-methylbenzophenones afford anthracene derivatives in low yields while others, under the conditions investigated, gave only negative results. Although 2,4-dimethylbenzophenone apparently failed to undergo cyclization under conditions adequate for the formation of a certain amount of 2-methylanthracene from the isomeric 2,5-dimethylbenzophenone, a corresponding difference was not noted with the 2,4,4'-and 2,5,4'-trimethyl compounds.

Table I includes an instance of the elimination of an isopropyl group in the course of the pyrolysis and an example of the formation of an authrone derivative along with the corresponding hydrocarbon. The anthrone may possibly arise by the dehydrogenation of the postulated intermediate dihydroanthranol. The last entry of the table shows that cyclization can occur in both of two possible directions, the one involving an ortho methyl group and the other an ortho methylene substituent.

1,2,5,6-Dibenzanthracene Series (Table II). The Elbs reaction affords by far the most rapid and economical method known for the synthesis of 1,2,5,6-dibenzanthracene (III), a hydrocarbon widely used for the experimental production of cancer in animals. A number of points of general interest have been discovered in the extensive studies of this example of the reaction. One is the occurrence of a rearrangement in the pyrolysis of α,α' -dinaphthyl ketones. Although 2'-methyl-2,1'-dinaphthyl ketone (I) and 2-methyl-1,1'-dinaphthyl ketone (II) would be expected to yield isomeric hydrocarbons, $^{12,-10}$ Cook 24 showed that they both afford III as the chief product. Cook suggested that the ketone

III (coloriess)

IV (reliow)

TABLE II

1,2,5,6.Direveanthracene Demoatives

	>) -			1
2,1'-Dinajhthyl	Preparation	Pyrolysis	1,2,5,0-fylienzantliraceni Derivativo	Yield, % caca	Teler-
Methyl	ArCOCH ArTI	Reft 20 min.	1,2,5,0-Dibenyanthraceno	Aleut 20 32	22
	ACCOS + ACCOS (30%)	<u> </u>	1,2,5,0-Dilenenthreens	§ ~	2.5
hydro Tythyl	ArCOCI + Ar'H (91% erude)	425-430°, 14 hr.	(delaydrogenation) 1,2,5,0-Dibenranthraceno	ន	23
r.y.Dimethyl	Arcoct + Ar'11 (31/2) Arcoct + Ar'11 (76/2) Arcoct + Ar'11 (19/2)	415°, 2 hr. 1-Methyl Refl 2 hr. 3-Methyl Refl 440-150°, about thr 2"-Methyl	1-Methyl 3-Methyl 2'-Methyl	- 8 -	222

TAIILE II-Continued

Synthery of Other Polynuclean Ilybnocarbons from Monoretones

1	1.1		9,000	
	8-1-10°	10' (Hener.) +'		•
	- (8/ 		;

t,1'-Dinaphthyt Kotano Derivativo	Preparation	Pyrolysis	1,2,5,6-Dibenzanthracene Derivative	Yield, Ço	Refer- ence
2-Mothyl	Arcoci + Ar'II	Refl. 20 min. Refl. 5 hr.	I,2,5,6-Dibenzan(hracene	About 20 19, 9	19, 9 10, 9
2,4'-Dimethyl	ArCoci -+ Ar'II	4.40-450°, about 1 hr.	1,2,5,0-Dibenzanthracene		57
2,6-Dimethyl	Arcoct + Ar11 (50%)	440-450°, whout I hr.	3'-Methyl	٠-	12
2,7-Dimethyl	Arcoct + Ar1t (70%)	4:10-150°, about 1 hr.	2'-Methyl	٠-	7
2',3'-Dimethyl	Arcoci + Ar'II	4.15°, 2 hr.	4-Mc(hyl	~	: :
2,4',7'-Trimothyl	Arcoci + Ar'11	410-150°, ahout 1 hr.	2'-Mathyl (loss of CH3)	۲.	7.
4,2',6'-Trimothyl	Arctoca + Ar'11	4:10-150°, ahout 1 hr.	31-Methyl (loss of CIIs)	c	7.
4,2',7'-Trimethyl	Arcoci + Ar'11 (45%)	.140[50°, nbout 1 lir.	2'-Methyl (loss of CIIs)	ç	7.
2'-Methyl-1',5'- dinethylene	ArCOCI + Ar'II (65%)	430-450°, 1-2 hr.	Phenau(hrancenaphtheno	9	ដ

				1,	2,5,6	DIB	ENZ.	ANTHE	LACE	NE S	SERII	ES
19, 25		254	254	23	25	254	2	254		58	21	27,28
-		22	12	٠.	•-	23	24	2 2	•	•-	35	1
1,2,3,4-Dibenzanthracene, 2,3-(Naphtho-2',3').phe-	2',3')-phenanthrene	1,2,3,4-Dibenzanthracene	6-Mcthyl-1,2,3,4-dibenzan-	2,3-(Naphtho-2',3')-phe-	2,3-(Naphtho-2',3')-phe-	2,3-(Naphtho-2',3')-phe-	1,2,3,4,5,6-Tribenzanthra-	cene 2',3'-Phenanthra-2,3-phe-	2',3'-Phenanthra-1,2-an-	thracene 2',3'-Phenanthra-1,2 an-	thracene 2,3-Phenauthra-3',2'-(or	1,2'.3-Naphtha-1,2-pyrene
Refi.		400-420° with Zn, 3 hr.	420°, 23 hr.	Reft. with Cu, 20 mis.	Refl. with Cu, 20 min.	400-420° nith Zn, 2 hr.	Refl. 2 hr.	410° with Zn, 23 hr.	430-440°, 3-2 hr.	Reft. 20 min.	430-450°, 3-2 hr.	420-440°, 2 hr. 2',3'-Naph
o-CeH4(CH3)COCI + Phenan- threne		9-0-1040 phenshing CHAMEA + CARCON (83%)	CHIMIES + CIMISCINIS %)	C,oH,COCI + Tetralia	CıcH₁COCı + Tetralia	3-Tolus iphenanthrene C, HtMgX + C, tH, CN (79%)	2-Methyl-1-(9'-phenan- Carl'yCOCI + Caclificity throyl)-caphthalene	C1.II.MgX + C1.II.CIN.(65%) 410° with Zn, 22 1 C1.II.COCI + Calls.(CII.)MgB	A-ClaHoCOCI + CroHs(CHa)	ACAH,COCI + CAH,CH,	CtoH4(CH4)COC! + CtoH10	o-CH ₂ C ₂ H ₁ COCI + C ₁₈ H ₁₀ 378 (1929).
Ketone mixture	O or Walter Parketon Library	9-0-1 ottly tynenanthrene	zovi)-obenanthrene	2-Methyl-3-(f'-naph- thoyl)-tetraln	2-Methyl-3-(2'-naph-thoyi)-tetralin	3-Tolus lphenanthrene	2-Methyl-1-(9'-phenan- throyl)-naphthalene	2-Mothyl-1-(3'-phenan- throvi)-naphthalene	2-Methyl-1-(1'-an- throyl)-naphthalene	2-Methyl-1-(2'-an- throjl)-nsplithalene	2-Methyl-1-(2".fluo- renyl)-naphthalene	3-Toluylpyrene CH3C4H

.

Dachmann and Peresc. J. Am. Chem. Soc. 99, 2339 (1937).
 Wutzerier and Schön. Z. Patrick. Chem., 230, 146 (1934).
 Cook and Breett. J. Chem. Soc., 338 (1933).
 Char, Ber. 62, 1671 (1939).

4 Clar, Ber, 62, 1574 (1929).

Flower and Novemen, J. Am. Chem. Soc., 58, 2376 (1939).
 Cook, J. Chem. Soc., 1892 (1933).
 Cook, J. Chem. Soc., 489 (1931).

19 Bachmann, J. Org. Chem., 1. 347 (1937).

11 Cook, J. Chem. Soc., 499 (1931).

(II) which reacts abnormally may undergo rearrangement to the isomer I at the pyrolysis temperature, and indeed it has been shown ¹⁰ that the abnormal pyrolysis of II proceeds far more slowly than the normal condensation of I. The several examples listed in the second section of Table II demonstrate the generality of the rearrangement.

The hydrocarbon prepared from either ketone retains a bright yellow color not altered by distillation or repeated crystallization, 19 10 but Cook 9 found that pure 1,2,5,6-dibenzanthracene is colorless and that the color is due to the presence of a persistent chrysogen which Winterstein and Schön 25 later identified as the isomeric 1,2,6,7-dibenzanthracene (IV). The chrysogen, which evidently arises from the ketone I by condensation of the methyl group into the β -position of the second naphthyl nucleus, constitutes about 10% of the hydrocarbon mixture. Various methods have been reported for the removal of the yellow contaminant based upon its greater affinity for chemical reagents or adsorbents. These include (a) preferential sulfonation of the mixture in xylene solution 20 (extensive losses), (b) chromatographic adsorption 25 (10-20% recovery), (c) treatment with malcic anhydride in boiling xylene, 22 and treatment with lead tetracetate in acetic acid solution 20 (70-83% recovery).

In this series there are several instances of the loss of methyl groups in the course of the Elbs reaction. The pyrolysis of the ethyl-substituted ketone V affords 1,2,5,6-dibenzanthracene in relatively high yield, the

methyl group which normally would appear at a reactive meso position of the product being completely eliminated. 1,1'-Dinaphthyl ketones having methyl groups at the 4- or 4'-positions (VI) are prone to lose these substituents, and there appears to be a general tendency for the elimination of substituents from α -positions in the carbonyl-containing rings of the dinaphthyl ketones.²¹ Another change observed in the course of a pyrolysis is dehydrogenation. The 5,6,7,8-tetrahydride of

²³ Cook, J. Chem. Soc., 3273 (1931); Cook, Hieger, Kennaway, and Mayneord, Proc. Roy. Soc., B111, 489 (1932).

Fieser and Hershberg, J. Am. Chem. Soc., 60, 1893 (1938).
 Fieser and Peters, J. Am. Chem. Soc., 54, 3742 (1932).

the ketone I affords the fully aromatized hydrocarbon III when heated at 430-450°, and other instances studied by Clar. are listed in the third section of Table II, which includes data on the synthesis of higher polynuclear bydrocarbons by elaboration of the general scheme already illustrated.

1,2-Benzanthracene Series (Table III). The most noteworthy feature of the data on the conversion of methylated benzoylnaphthalenes into 1,2-benzanthracene derivatives is the striking contrast in the behavior of the 2-methyl and 2-methyl compounds, VII and VIII. The first ketone on being pyrolyzed for three hours affords 1,2-benzanthracene in as high as 61% yield, whereas the isomer VIII loses water only in the course of twenty-six hours and gives the same hydrocarbon in 10% yield.

The difference is understandable in terms of the mechanism suggested by Fieser and Dietz, for in the favorable case (VII) the methyl group condenses into a naphthalene uncleux, while in VIII this group must substitute into a less reactive benzene nucleus. Cook's postulate that the Elbs reaction is dependent upon a process of enolization does not explain the observed difference, since VIII should be more prone to enolize than VII.

The favorable feature of structure encountered in o-tulyl a-naphthyl

ketone (VII) is met with also in the series of o-methyl 2.1'-dinaphthyl ketones listed in Table 11, for example ketone 1 (p. 131), and in this series the yields again are on the whole definitely better than with the methylated benzophenones (Table 1) Ketones of the type of I-benzoyl-2methylnaphthalene (VIII) thus fall into the same unfavorable class as the benzophenone derivatives, and it will be seen from the data of Table III, which refer almost entirely to ketones of the type of VIII, that the yields are regularly poor Unfortunately polysubstituted ketones having the o-methyl group in the naphthalene nucleus are more readily accessible than the more favorably constituted isomers and have been used exclusively for the synthesis of 1,2-benzanthracene homologs. In this series aroyl rearrangements occur in several instances, and there are examples of the loss and degradation of alkyl groups. Methyl substituents have been found to be channeled from positions 5 and 8 of the resulting 1,2-bear inthracene, but there are examples of the retention of methyl at these same positions as well as at positions 4, 6, 7, 2', and 3'

TABLE III

		/ -	1/2
1,2-Benzantunagun Dentaativis	s	\	<u>{</u>
RACHINE DI		-/	
Benzantu	- V	<u>*</u>	-
1,2	_	5\ -	

)6	7		
			1.9-Benzanthraceno	Ylold, %	Keter-
1'-Bengoylnaph-	Prominition	Pyrolyala	Derivativa		outed
thatene Derlyntive			1 o Havenethencono	20	30
Military County of Section (Section Section Se	1.CN 1. ArWhelle (7893)	410° with Zu, 3 hr.	1,21	ษ	# S
2-Mothyl	WOW I WINDLY	400-410° with Za, 3 hr.	1 9-Honzanthraceno	91	
2'-Methyl	Arcoci 4- Ar'II	125-400° with Zn, 2 hr.	5-Mothyl, 8-mothyl, and	Low;rourr.,	A
2,3-12imethy1		:	1.2-Benzanthracono (1088	2-10	표
2,2'-Dimethyl	Arcoci + Arill	See note a	of C11a)	2-10	풇
- -	11.4V 17.1000	See noto a	7-Nethyl	01-2	돐
3,2'-Dimethyl	MCOCH + MH	See note a	0-modayr	10, total	ਜ਼
o, 3'-1 hinethyl	Arcoci + Ar11 (70%)	12 cm. 3-4 hr.	1.2-benzanthrono		:
		1 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	4-Mothyl 4 maphthacone	.	3
		.115°, 5 nr.	"Yan belief	2-10	; ;
" o' a'-Dimethyl	Arcoci + Arti	See note a	12/10/12	2-10	<u>ج</u>
"" (1.71)imothyl	Arcoci + Arti	See note 4 	6-Isopropyl 4- 6-mothyl	7	
4-180propy 1-2'-methyl	Arcoch + Ar'11	, 107-01-	(degradation of i-1'r)		ŗ
			G-Phenyl	x :	= =
4-Phenyl-2'-mathyl	Arcoci + Ar'11 Arcoci + Ar'11	Keal. 5 al.: See note a	6,7-Dimethyl	01-9	<u>.</u>
Chamber - Erick					

g 3

	Arcoci + Arii		3',7-Dimethyl	_	34
	Arcoct + ArtI	See note a	2,7-Dimethyl	2-10	34
	Arcoct + Arti	See note a	3',6-Dimethyl	5-10	34
4,2,7Trimethyl	Arcoci + Arti	See note a	2,6-Dimethyl + 2,7-	5.10	34
4-Isopropy]-2.7*-	Arcoct + Arti	Sernole	demethyl (rearr.) 2'.7-Dimethyl (degrad	5-10	34
dimethyl 2-Methyl-4.5'-dimeth-	dimethyl 2-Methyl-4'.5'-dimeth- ArCOCI + ArTI (23%)	400-410°, 40 min.	rearr.)	ន	355
3,4-Trimethylene-2. RII + Ar'COC	RII + Ar'COCI	450°, 2 hr.	5.6-Cyclononteno (+ 6.7-		1,2
methyl			isomer?)		-B

	Re	RELATED EXAMPLES			
Ketone	Preparation	Pyrolysis	Product	Yiold, % Refer-	Refer-
4,4'-Di-a-naphthoyl-	3.3dimetalluluman	430-450°, 2 br.	1,2,1',2'-Dibenz-6,6'- (or	22	12
ric. a. Xylyl Ponghthoyl	ric Nyly Frachthoy? ArCN + Ar MgDr (87%)	420-425" nith Zn, 11 br.	420-425 "with Zn, 1 htr. 8-Methyl. 1,2-benzanthra-	Low	33
1-lienzoy lacenaphthene	1-thenroy lacenar htthens Call MRBs + Ar'CONIIg (05%) 420-425°, 40 min.	420-425°, 40 min.	1,9-Methylone-1,2-benzan-	13	83
			thracene		

[•] In the series of experiment Cook the factor and write was no longer evolved and building council, the product was conducted in 440-450° for the four four or semiclame longer. The yield of rocks married that it is the four to purchase longer. The yield of rocks married was 25,25%, the yield of product purched by desirations, crystalline.

420-425 with Za, 1 hr. 4"Aza-1,3-benzanthracene

ArMr.Br + Ar'CN (33%)

5-Qunotyl o-talyl krione

²¹ Freer and Herablerg, J. Am. Chem. Soc., 59, 2503 (1937). Los, and (usually) through the pierate was 6-1972

¹¹ Tree and Canon. J. Am. Chem. Soc., 61, 1740 (1939). M Cook, J. Chem. Soc., 456 (1932).

Frence and Herabberg, J. Am. Chem. Soc., 62, 1640 (1910). Geyer and Zuffantl, J. Am. Chem. Soc., 57, 1787 (1935). "Cook, J. Chem. Soc., 2529 (1931).

An isopropyl group was in part retained at position 6 and in part degraded to furnish a 6-methyl group.

Synthesis of Cholanthrenes (Table IV). The synthesis of a hydrocarbon of the cholanthrene series by the Elbs reaction is illustrated by the formulas shown in Table IV. Although singly linked alkyl substituents are often eliminated at the pyrolysis temperature from the 5- and 10positions of the 1,2-benzanthracene nucleus, the nee- or dimethylene bridge attached at these points appears to be more stable, for no instance of a rupture of these linkages is on record. Furthermore, both the 4-hydrindyl-α- and β-naphthyl ketones present structures particularly favorable for the Elbs condensation. As with o-tolyl a-nauhthyl ketone (VII), ring closure involves a substitution into a reactive naphthalene nucleus, and another auspicious circumstance is that the ortho methylene group undoubtedly surpasses a corresponding ortho methyl group in reactivity. It is thus understandable that the reaction resulting in the formation of a cholanthrene takes place with particular rapidity and probably at a slightly lower critical pyrolysis temperature than in any other known example.

The generally favorable situation is reflected in the fact that the important eareinogens cholanthrene and 20-methylcholanthrene can be prepared in quantity in a thoroughly purified condition in 40-50% yield and that the yields on the whole are definitely better than in any of the other series studied. Methyl groups at the 1-, 6-, and 7-positions of the hydrindene nucleus pass through the pyrolysis unscathed, and the same is true of a methyl situated in the naphthalene nucleus at the $4'(\alpha)$ -position, whereas in the synthesis of 1,2,5,6-dibenzanthracenes such a group invariably is eliminated. The only troublesome instance of methyl elimination encountered is in the pyrolysis of 2,7-dimethyl-1-(α-naphthovl)-hydrindene, when the alkyl group which should appear at the highly reactive meso-methylene group (C15) was retained only in part, and was in part lost. Syntheses of the 20-ethyl, 20-isopropyl, and 20-tbutyl derivatives have been accomplished successfully, if in low yield. It has even been possible, at least in some instances, to earry methoxyl groups and halogen atoms through the synthesis. A methoxyl substituent located at either the 6'- or 7'-position of the ketone is retained admirably, and the corresponding 3- and 2-methoxycholanthrenes are obtainable in excellent yield. A methoxyl at the vulnerable 4'(a)position, however, is completely lost. With a chlorine atom at the 4'position of the naphthoylhydrindene, extensive elimination of the substituent also occurred, but careful fractionation of the reaction mixture afforded a small amount of 6-chloro-20-methylcholanthrene. The 3chloro isomer was obtained without difficulty.

The second section of Table IV lists a number of variations of the cholanthrene synthesis. The ketones IX and X afford the expected at ',9-dimethylene-1,2-benzanthracene and 15,16-benzahelydrocholanthrene in 32% and 60% yield, respectively. The particularly high yield

in the latter case probably is associated with the presence in X of a doubly activated methylene group. The ketone XI is convertible into 4,10-aco-1,2-benzanthracene, an isomer of cholanthrene. That the yield is only 10% is attributable to the fact that the condensation involves substitution into the benzene rather than the naphthalene nucleus. ar-ar-Tetrally a-naphthyl tetone (XII) would be expected to yield homocholanthrene, but it affords instead 1,12-trimethylenechrysene (XIII), evidently as the result of a disproportionative isomerization to an aromatic structure of greater stability

Another variation consists in the use of certain aryl quinolyl ketones for the synthesis of polynuclear aromatic substances containing a condensed pyridine ring. Thus 5-quinolyl '-methyl-4-hydrindyl ketone (XIV) on pyrolysis affords 20-methyl-4-nacholanthrene (XV) in 12%

CHOCANTHRING DERIVATIVES

	Refer-	% & Q	हो हो ह	1=94	5 5	ž č	###
Cholantinus Denivatives Cholantinus Denivativ	Yield, %	등학~	About 50 49	18 m a	់ឥត	20 (23, total)	ន្តត
	Cholanthrene Detivative	Cholanthreno	20-Methyl	20-Ethyl 20-fsopropyl	20-7-may- 22-Nethyl 0-Nethyl	16,20-1)imethyl 15,20-1)imethyl -l- 20-	metnyi 6,20-1)imethyl 6,22-Dimethyl
	Pyrolysis	.100105°, 25 min.	.405410°, 3 lir. .405410°, 25 min. .405410°, 40 min.	405-410°, 40 min. 405-410°, 4 hr. 410-415°, 30 min.	-400110" -415	.100105°, 30 min.	-110° -110°
	Preparation	Arnight 4- Arcoci (50%) Arcn 4- Arnight (91%)	Mixt. from e- and p-Calloffr ArMgBr ArCOCI (60% 9) ArCN ArMgBr (80%)	ArMflir + Ar'CN (49%) ArCN + Ar'Night (41%) ArCN + Ar'Night (82%)	Archale + Arco (46%) Arco + Arman (94%) Arco + Arman (86%)	Armen + ArCOCI (60%) Armen + ArCOCI (48%)	Arli + Arcoci (low) Araight + Arcn (si?) Arcn + Arnight (s0%)
	4-(r-Naphthoyl)- hydrindene Derivative	Parent ketono	7-Methyl	7-16/15/1 7-18/15/19	7-6-Butyl 6-Mothyl 4'-Mothyl	1.7-Dimethyl 2,7-Dimethyl	7.4'-Dimethyl 6.4'-Dimethyl

				s	YNTI	tesis c)r (CHO	LANT	HRE	VES			
8	25	38	23	23		Refer-	8	ę	S	23	33	33	25	
ī	38	9		ĸ		Yeld, 75	-	8	æ	g	21	ន	g	
20-Methyl (lose of OCII,)	3-Methoxy-20-methyl	2-Methoxy-20-methyl	6-Chloro-20-methyl + 20-	3-Chloro-20-methy1		Product	8,9-Dimethylene-1,2-ben-	ranthracene 7-Methyl-S,9-dimethylene-	1,2-benzanthracene 4-Brome-7-methyl-8,9- damethylen-1,2-benzan	thracene 1.9-Dimethylene-1,2,5,6.	20-Methyl-4-azacholan-	threne 11-Hydroxy-20-methyl-1.	4,10-Acc-1,2-lyenzan- thracen	
405°, 15 min.	465°, 20 min.	405, 15 min., 420°	410°, brief beating	400°, 15 min.	Relate Exames	Py roly ais	400-405*	400-402*	370°, 8 min.	400-415", 15 mm.	410°, 3-4 mm,	100-410" with Pd-C,	405°, 45 ma.	
	Arta + Artagar (1652)	ANA + ArCOCI (18%)	Arch + Armigh (72%)	ArCN + Ar'MgBr (6352)	26	Preparation	ArMgBr + ArCOCI (49°2)	ArMalle + Arcoct (45%)	Arch + Ar'Night (50°2)	Arla + Arcoct (217.)	MIL + ACCX (17.5°2)	Armelle + Arcs (37%)	Tetrahydrale + Se (69%)	
7-Methyl-4'-methoxy	7-Methyl-6-methoxy	ь	L.Methyl-V-thloro	7-Methy 1-6'-chilom		Ketene	4-(A-Naphtheyl).	+ (ANaphilos)).7.	7-Methyl-t-(3-bronce	1-(m-Naphthoyt).	S.Quindyl 7-methyl-4.	SQuinelyl 7-methyl-4- hydrodyl ketone	- Pentoy - 2.3-cyclo.	The same of the sa

Note: References 24-45 appear on p. 166.

TAIRIS IV-Continued Relation Brancing

					Rofer-
manager and the control of the contr	10) Louise Co	Pyrolysla	Product	Yield, % onco	oneo
Kelone			-01,1-orbydrahy1.1. 17 10.10	-	<u> </u>
5-Benzayl-0,7-ayelo-	Arcoci - Ar'11 (90%)	.110°, 1 hr.	nce-1,2-benzanthracene-	12-21	
hensementann			yleneisobenzanthrene-2	8	38
. Carphland).	Arcoct + Call MgBr (50%)	.115°, 25 min.	15, 10-15chzdeny droenement		ğ
(horen)	Carso to to a second	.115°, 25 min.	1,2'-Naphtho-1,2-imoreno	•	
1-(p-Naphthoyl)-	Arcoci + Caus (ar. 20)	17	L.12-Trimethylenedryseno	¥	23
ar-a-Totralyl a-naph-	Arneib 4 Arcoci (40%)	O. (ON)-(01)	a way and adone ? I hours.	<u>.</u>	25
thyl ketono ar-a-Tetralyl B-naph-	Armen + Arcoci (44%)	.100", 30 min.	She transfer of the state of th		
thyl ketono			Homers and a dehydro		
					_

34 Figure and Solfana, J. Am. Chem. Soc., 57, 2174 (1935), 39 Bachman, J. Ors. Chem., 3, 434 (1939).

Bruce, J., Am. Chem. Soc., 63, 301 (1941).
 Bruce, J., Am. Chem. Soc., 60, 2277 (1938).
 Pieser and Seligman, J. Am. Chem. Soc., 67, 942 (1035).
 Pieser and Seligman, J. Am. Chem. Soc., 68, 2482 (1930).

44 Brave and Kahu, J. Jin, Chem. Soc., 60, 1017 (1938).
44 Brave and Todd, J. Jin, Chem. Soc., 61, 157 (1939).
46 Pigace and Stow, J. Am. Chem. Soc., 60, 170 (1938).

4 Pieser and Bowen, J. Am. Chem. Soc., 62, 2103 (1940).
4 Pieser and Selignan, J. Am. Chem. Soc., 67, 1377 (1935).
4 Pieser and Selignan, J. Am. Chem. Soc., 69, 479 (1937).
50 Pieser and Deereux, J. Am. Chem. Soc., 60, 2265 (1938).
50 Pieser and Deereux, J. Am. Chem. Soc., 1825 (1937).

von constant Rhegel, J. Am. Chem. Soo., 59, 2561 (1937).
 Pileser and Rhegel, J. Am. Chem. Soo., 57, 1681 (1935).
 Pileser and Horshberg, J. Am. Chem. Soo., 59, 883 (1937).
 Pileser and Sollgaum, J. Am. Chem. Soc., 59, 883 (1937).
 Pileser and Sollgama, J. Am. Chem. Soc., 59, 178 (1930).

yield. Similarly, 5-quinolyl o-tolyl ketone (Table III) yields 4'-aza-1,2benzanthracene (β-anthraquinoline). With 8-quinolyl 7-methyl-4hydrindyl ketone the sole reaction product (50%) contains an atom of oxygen and presumably is of a stabilized anthranol true of structure.

Pyrolysis of Diketones (Table V). The Libs reaction has been applied rather extensively, particularly by Clar and co-workers, to the synthesis from suitable diketones of higher hydrocarbons having two separate or merged anthracenoid groupings (see refs. 57-64 in Table V). One example is the pyrolysis of 4,6-dibenzoyl-1,3-xylene (XVI), which yields a phytocarbon having the probable structure of mesodihydropentacene (XVII). The formation of the dihydride rather than the fully aromatic

hydrocarbon doubtless is a consequence of the great reactivity of pentacene. The most extensive elaboration of the method yet accomplished is the synthesis of 2,3,8,9-di-(naphtho-1',2')-chrysene (XIX) from the diketone XVIII. The hydrocarbon, which metts at 500°, was

obtained in 52% yield. Other examples listed in the table involve diketones which are similar to XVIII but in which one or both naphthoyl groups are replaced by bouzoyl taillouls.

Summary of Side Reactions. Evanuation have been cited in the foregoing sections of the occurrence of anyt infrartions in the course of the Elits pyrolysis, of the climination of alkyl, bale, and methoxy substituents, of the degradation of supropyl to methyl, and of processes of hydrogenation, dehydrogenation, and intransolveniar disproportionation. The formation of antinuous in three behaves represents the production of substances of a stage of additional ligher than that of the expected hydrogenation, and there is one landmen of an apparent redution. As a hy-product in the synthesis of methylcholanthene, there was isolated of a substance which is resistant to dehyllogenation and which between 1-acenaphthyllithium and α -naphthoyl chloride, which was found at least more satisfactory than the attempted condensation of 1acenaphthylmagnesium iodide with the acid chloride. Yields reported for the reaction ArLi + ArCN are 51%, 18 50%, 51 and 17.5% 37 (eyanoquinoline), and the synthetic method thus appears less advantageous than the condensation of a Grignard reagent with the nitrile.

Selection of Conditions for the Pyrolysis. Attempts to find a catalyst for the Elbs reaction have met with little success. Elbs 5 tried sulfuric acid, potassium bisulfate, phosphorus pentoxide, and zinc chloride with negative results. Morgan and Coulson 15 found piperidine and acetic anhydride also without effect and noted that 2,4,4'-trimethylbenzophenone is cleaved by sulfuric acid to p-toluic acid and m-xylene.

The pyrolysis frequently has been conducted in the presence of a small amount of zinc dust, and indeed in the first instance of the reaction Behr and van Dorp 1 passed the vapor of o-tolyl phenyl ketone over zinc dust. It is still questionable that the use of zinc results in any material improvement. In two sets of parallel experiments 33, 54 conducted with and without zinc dust no difference was observable in the results. In the synthesis of the 2-50 and 3-methoxy 52 derivatives of methylcholanthrene the yields in small-scale experiments were 36 and 38% in the presence of zinc and 40 and 32% in its absence. It was observed by Hershberg 22 that o-tolyl α -naphthyl ketone can be pyrolyzed at 400-410° in the presence of zinc dust to give 1,2-benzanthracene in 61% yield, but that without zinc the reaction proceeds only very slowly at the same temperature. This is the only concrete indication that zinc has any effect, and the effect may be merely to lower slightly the pyrolysis temperature. A comparison of the first three entries in Table III would seem to indicate that the use of zinc improves the yield in the synthesis of 1,2,5,6-dibenzanthracene, but in view of the experiment cited below as an example of the procedure it is probable that the higher yield reported by Bachmann 20 is attributable more to his use of homogeneous Grignard ketone in place of the mixture resulting from the Friedel and Crafts reaction.

Although many of the earlier experiments were conducted by heating the ketone over a free flame at the boiling point without control or measurement of the temperature, most workers now consider it advisable to use a heating bath and to conduct the pyrolysis at the lowest temperature at which a steady liberation of water is observed.^{34, 43} As the bath temperature is brought slowly to or above 400°, the critical pyrolysis temperature usually is sharply defined by a brisk bubbling which is hardly noticeable at a temperature 5° lower. 43

Certain claims concerning modifications in the procedure of conducting

the Elbs reaction have appeared in the patent literature, ¹²⁻⁹⁷ but the supporting data are not sufficiently definitive to warrant acceptance of the claims in the absence of confirmatory evidence. Thus it is stated ⁴⁴ that ketones can be pyrolyzed to hydrocarbons by dropping the liquid into a metal tube næked with active carbon, alumina, or silica gel at about 400°, but there is no indication that the contact agents play any real role or effect any improvement.

Two isolated and as yet unclarified instances are reported of the use of starting materials other than ketones. Elbs found that, although mylyl phenyl ketone failed to undergo satisfactory reaction, the corresponding alcohol, m-vylyl phenyl carbinol, condensed to θ -methylanthraceno almost as readily as θ -xylyl phenyl ketone. On ovidation of θ -amphthyl-i-(7-ethylhydrindenyl)-carbinol, Bruce and Kabn " obtained an abnormal product regarded as an ether, ArCH(Ar')OCH(Ar')Ar, and this on pyrolysis afforded 20-ethylcholanthrene.

Example 1. 1,2,5,6-Dibenzanthracene (Experiment by J. Cason). For best economy, and because of the greater speed and ease in the manipulation of large amounts of material, it is considered advantageous to employ the ketone mixture prepared by the Friedel and Crafts reaction, in even though the yield in the pyrolysis may be lower than with the nurse Grimant ketone.

A 2-1, three-necked flask is charged with 1.02 moles of β-naphthoic acid and 1.04 moles of phosphorus pentachloride and the mixture heated for one hour on the steam bath. Boiling chips are added, and the phosphorus oxychloride is taken off at water pump vacuum. The residue, which crystallizes on cooling, is dissolved in 575 co of carbon bisulfide, 1.23 moles of β-methy(naphthalene is added, and then, while the mixture is stirred mechanically under reflux, 1.31 moles of aluminum chloride is added during thirty minutes. The mixture is refluxed for two hours, rooked, decomposed with fee and hydrochloric acid, and the solvent is removed with steam. The granular brown solid is digested at the boiling point with sodium carbonate solution, collected, and dried thoroughly at room temperature (it becomes gummy at 50°; a trace of water causes troublesome foaming in the distillation). Vacuum distillation gives 264 g. (88%) of crude ketone, b.p. 230–262°/4 mm. (bath, 300–310°). The distillate is a clear, dark reddish of which sets to a glass on cooling.

The pyrolysis is conveniently carried out in a two-bulb distillation flask 68 having a 300-cc, distillation bulb with an inverted-U side arm

I. G. Farbenindustrie, Brit. pat., 251,270 (1926) [C. A., 21, 1272 (1927)]
 I. G. Farbenindustrie, Brit. pat., 253,911 (1925) [C. A., 21, 2478 (1927)]

Nicodemus and Berndt, U. S. pat., 1,776,924, 1,776,925 (1930) [C. A., 24, 5765 (1930)]
 Fieser, "Experiments in Organic Chemistry," 2nd ed., p. 250, D. C. Heath and Co. 1941.

TABLE V

PYROLYSIS OF DIKETONES

No condensation No condensation No condensation No condensation No condensation Dihydropentacene (nrobably meso 64) [12-(Naphtho-2-37)-anthracene (n) and bihydropentacene (n) and yery low anthracene (n) and anthracene (n) and (n) and (n) and (n) anthracene (n) anthracene (n) and (n) anthracene (n) anthr					
No condensation Dilydropentacene (probably meso **) (1,2-(Naphtho-2',3')-anthracene (a) and (2,2-25, total lapydropentacene (b) (7,7'-Dimethyl-1,2-(naphtho-2',3'-anthracene (a) and (2,2'-Dimethyldhydropentacene (b))	Diketone	Product	Yield	Remarks	' ' 1
(4) (2) (3) (4) (4) (5) (7)		No condensation Dilydropentacene (probably meso 18) [1,2-(Naphtho-2',3')-anthracene (a) and [2,7'-Dimethyl-1,2-(naphtho-2',3'-anthracene (a) and [2,2'-Dimethyl-1,2-(naphtho-2',3'-anthracene (',7-Dimethyl-1,2-(naphtho-2',3'-anthracene (',7-Dimethyl-1,2-(naphtho-2',3'-anthracene (',7-Dimethyl-1,2-(naphtho-2',3'-anthracene (',7-Dimethyl-3,-i-henzpeutaphene (') [2,2-(Anthraceno-2',1')-anthracene [Bexaphene No condensation 4,5-Benz-10,11-(1',2'-anthracene 2,3,8,9-Di-(naphtho-1',2')-chrysene	20–25, total Very low ? ?	Rearr. (b) Rearr. (b) Rearr. Rearr.	56 57 57 59,60 59,60 59,60 61 61 61 63,64 63,64 63,64 63,21 21 21 21
0.12		60 2			

" For nomenclature, see Clar, ref. 62.

44 de Diesbach and Stretzel, Heft. Chim. .tcla, 8, 556 (1925).

14 Clar and John, Ber., 63, 2967 (1930). 17 Char and John, Her., 62, 3021 (1929).

⁴³ Ctar, John and Hawran, Ber., 62, 940 (1929).

13 Clar and John, Ber., 64, 981 (1931).

⁶¹ Clar, Wallenstein, and Avenarius, Ber., 62, 950 (1929). 64 Clar, Ber., 73, 81 (1940).

52 Clar, Ber., 72, 2137 (1939). at Clar, Ber., 72, 2139 (1939).

probably is formed by the reduction of the carbonyl group of the starting ketone. Another side reaction beads to the formation of hydrocarbon fragments such as phenanthrene from a phenanthryl aryl ketone, from an anthracen from an anthral aryl ketone. Apparently the ketone suffers some cleavage by the water evolved, perhaps with subsequent decarboxylation of the acid fragment: Λ TrOAr + H₂O \rightarrow ArCOOH + Λ ArI + Λ Or + Λ + Λ II + Λ

EXPERIMENTAL PROCEDURES

Preparation of the Required Ketones. The ketone required for a given Elbs synthesis is often obtained most readily by the Friedel and Crafts reaction, and in many of the experiments erted the practice has been to distill the total ketone or ketone mixture and submit it as such to pyrolysis. Since the distillate almost invariably consists of a mixture of isomers, this practice introduces uncertainties concerning the nature of the reaction and the yield. Except for the routine preparation of materials by known methods, it is definitely advantageous either to purify and characterize the products obtained by the Friedel and Crafts method or to employ a synthesis from a Grignard or lithium derivative.

The principal variations of this general synthesis have been studied carefully in a number of instances, as summarized in the second column of Tables I-IV. The reaction ArMgX + ArCOCI has been employed in 10 instances with yields ranging from 40 to 59% and with an average yield of 49%. Bruce " has found that considerable losses are associated with side reactions resulting in the formation of ArH and (ArCO)2O. The use of a nitrile in place of an acid chloride is definitely advantageous, for in 22 examples the reaction ArMgX + ArCN has given pure ketones in an average yield of 70%. Some of these syntheses represent particularly difficult eases, for example where a cyanoquinoline constitutes one component, and in the more normal instances the yields frequently are in the range 80-90%, particularly when the inherent slowness of the nitrile reaction has been recognized and adequate time allowed. The use of an amide as the second component has been investigated in only one instance, but with marked success. The condensation of phenylmagnesium bromide with 1-acenaphthamide was found to proceed slowly (72 hr.) but very smoothly, affording 1-benzoylacenaphthene in 95% yield." Lithium derivatives have not been employed at all extensively but, except in special cases, probably are less satisfactory than the Grignard reagents. The reaction ArLi + ArCOCI has given yields described as "very low," a 48%, a and 21%. The last figure applies to the reaction sealed on about 11 cm. above the flask and carrying a 100-cc. receiving bulb. The flask is charged with 152 g. of the crude ketone and heated in a nitrate-nitrite bath (care!) at 430° ± 5° (bath). The pyrolysis must be attended constantly and the upper part of the flask warmed occasionally with a free flame to prevent water from condensing and dropping back into the hot mixture. Sweeping of the vessel with dry nitrogen or carbon dioxide perhaps facilitates somewhat the removal of water but is unnecessary and offers no material advantage. The evolution of water slackens noticeably within about three hours, and after three and onehalf hours the flask is removed from the bath, some glass wool is pushed down into the bulb to promote even boiling, and the mouth of the flask is sealed off. The product is then distilled at 2-3 mm. pressure, the lowboiling material which comes over in a fore-run being removed from the receiver. The dibenzanthracene distils largely at a bath temperature of 300-320°, and in part on raising the bath to 400°. During distillation the upper part of the flask is kept hot with a free flame. By using a flask with a high side arm and distilling carefully, a clean distillate can be obtained and redistillation is unnecessary. The distillate is melted, poured (and rinsed) into a 4-1. flask, and dissolved in about 31. of boiling benzene. The solution is concentrated until crystallization sets in (about 1800 cc.). The yellow dibenzanthracene separating in the first crop and melting at 260-262° (cor.) amounts to 44 g. (31%). The material recovered from the mother liquor when recrystallized melts at 253-258° and weighs 4 g.; total yield of yellow product, 33%. Almost identical yields were obtained in 20-g. and 80-g. runs and in runs conducted with added zinc dust.

In one method for the preparation of colorless dibenzanthracene,²⁰ a warm solution of 2 g. of lead tetraacetate in 500 cc. of acetic acid is added in small portions to a warm solution of 10 g. of yellow hydrocarbon in 500 cc. of benzene, and the solution is refluxed gently for one hour. The solvent is then distilled slowly until the solution has been reduced in volume to 300-350 cc. On cooling, dibenzanthracene separates in completely colorless plates with a blue fluorescence in ultraviolet light, m.p. 265-266° (cor.) (purest sample, 266-266.5°). The recovery ordinarily amounts to 70-83%. With particularly poor samples of crude hydrocarbon a second treatment with lead tetraacetate may be required; this was true of a sample melting at 250-255°, from which the recovery of thoroughly purified material was 50%.

Example 2. 1,2-Benzanthracene. 25. 22 o-Tolyl α -naphthyl ketone is prepared 29 by adding 23.4 g. of o-tolunitrile to the Grignard reagent from 50 g. of α -bromonaphthalene in 75 cc. of ether and 75 cc. of benzene. The mixture is refluxed for eight hours, cooled, and hydrolyzed with ice

and 100 ce. of concentrated bydrochloric acid. The sparingly soluble ketimine hydrochloride which crystallizes from the two-phase system is collected by suction filtration and bydrolyzed by boiling with water for one hour. The ketone crystallizes from the cooled mixture and is distilled, b.p. 174°/0.4 mm.; yield 37.8 g. (76%). After crystallization from methanol the ketone melts at 59-61°.

For pyrolysis, 20 a mixture of 34 g, of the ketone and 10 g, of zinc dust is heated for three hours in a metal bath kept at 410°. The hydrocarbon is distilled from the flask at 0.4 mm, and crystallized several times from benzene-alcohol, giving 17.2 g, 634%) of yellow 1,2-benzanthracene. For the removal of chrysogen by Cook's method, 20 the crude hydrocarbon (17.2 g,) is refuxed with 1 g, of malcie anhydride in 50 ee, of benzene for three hours. The hot solution is then shaken with aqueous alkali and the benzene layer is filtered, concentrated to a small volume, and treated with alcohol, when colorless 1,2-dibenzanthracene crystallizes, mp. 155.5-157°.

In a repetition ²² of this experiment the crude hydrocarbon from the pyrolysis of 6 g, of ketone with 2 g, of sine dust was purified after distillation by passage through a tower of activated alumina in benzene solution. This afforded, after crystallization, a total of 2.75 g of colorless 1,2-benzanthracene, m.p. 159-5-160.5° (cor.), and 0 6 g of yellow product, mp. 159-160.5° (cor.), and 0 6 g of yellow product, and 10 g of yellow product of the pro

Example 3. Methylcholanthrene. 7-Methyl-4-(e-naphthoyl)-hydrindene is prepared by condensing the Grignard reagent from 195 g, of redistilled a-bromonaphthalene in ether-benzene with 120 g, of 7 redistilled a-bromonaphthalene and hydrolyzing the resulting ketimine hydrochloride in a boiling mixture of hydrochloric acid, acetic acid, and toluene. The yield of the ketone, obtained as a light yellow, viscous oil, bp. 211-214*/2 mm., is 194 g (89%)

The pyrolysis of 108.5 g of the ketone is conveniently conducted in three lots and the products combined for purification. In a 100-ce flask with a scaled-on receiving bulb a portion of the ketone is warmed over a with a scaled-on receiving bulb a portion of the ketone is warmed over a free flame and then placed in a preheated nitrate-nitrite bath and heated for forty minutes at a temperature at which brask bubbling is observed (405-410°, uncor.). In a typical 56.5-g run the water and hydrocarbon (405-410°, uncor.). In a typical 56.5-g run the water and hydrocarbon (collective products collecting in the receiver amounted to 6 g. At the cleavage products collecting in the receiver amounted to 6 g. At the collection of the period of heating the flask is removed from the heating bath, and of the period of heating the flask is removed from the heating bath, and of the priod of the period of heating the flask is removed from the heating bath, and of the priod of the period of heating the flask is removed from the heating bath, and the hydrocarbon is distilled rather rapidly at 2-3 mm. pressure, and then redistilled to remove traces of entinined tar.

The redistilled material from the three pyrolyses consists of a bright

yellow solid weighing 113.3 g. This is dissolved in 400 cc. of benzene and the solution is cooled slightly and diluted with 1 l. of ether. The bulk of the methylcholanthrene separates in a nearly pure condition as fine yellow needles (72 g.). This is dissolved in 500 cc. of benzene, and 300 cc. of ether is added; on cooling, the hydrocarbon separates as yellow needles of high purity (63 g.), m.p. 178.5–179.5° (cor.) (purest sample, 179.5–180°). The mother liquor from this crystallization when concentrated and treated with 12 g. of pieric acid affords 12.5 g. of methylcholanthrene pierate, m.p. 176–177°. The oily material recovered from the original mother liquor is pyrolyzed again and the product distilled, crystallized once from benzene-ether, and converted to the pierate in benzene solution. Recrystallization affords 14.5 g. of satisfactory pierate, m.p. 178–179°. The total yield of material collected as such or as the pierate is 77.1 g. (49%).

CHAPTER 7

THE CLEMMENSEN REDUCTION

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INTRODUCTION

The replacement of the oxygen atom of the carbonyl group in an aldehyde or ketone by two hydrogen atoms through the use of amalgamated zinc and hydrochloric acid was first employed in 1913 by Clemmensen and is known as the Clemmensen method of reduction. The process has been applied to a large number of aldehydes and ketones as a step in the synthesis of polynuclear hydrocarbons and alkylated aromatic compounds, including those containing one or more phenolic hydroxyl groups. It has also played an important role in the elucidation of the structures of highly complex natural products.

The formation of hydrocarbons from aldehydes and ketones by the Clemmensen reaction can be illustrated by the following equations:

$$\begin{array}{c} \text{RC-H} \div 4(\text{H}) \xrightarrow{Z_2 \cdot \text{Hg/s}} \text{RCH}_2 \div \text{H}_2\text{O} \\ \\ \text{RC-R'} \div 4(\text{H}) \xrightarrow{Z_2 \cdot \text{Hg/s}} \text{RCH}_2\text{R'} \div \text{H}_2\text{O} \end{array}$$

The method is of peculiar value because nearly all other reducing agents which have been employed convert aldehydes and ketones to the corresponding carbinols or pinacols, rather than to the hydrocarbons. The chief alternative methods of accomplishing the same transformation are catalytic hydrogenation and reduction with hydrazine and alkali (Wolff-Kishner method).

The mechanism of the reduction by amalgamated zinc and hydrochloric acid is not clearly understood. If the carbinol is assumed to be the intermediate, then these same reagents should be suitable for the replacement of an alcoholic hydroxyl group by a hydrogen atom. However, with iew exceptions, alcohols are not affected by zinc amalgam and hydrochloric acid. Only activated alcoholic hydroxyl groups, such as those in β -hydroxy acids and benzyl alcohols, are removed by the Clemmensen reagents.

The wide use of this method of reduction has resulted in the development of several modifications of the original procedure. These consist

¹ Clemmenson: (c) Ber., 45, 1828 (1912; (b) Ber., 47, 51 (1914; (c) Ber., 47, 681 (1914).

primarily in the addition of solvents, in some cases miscible and in other cases immiscible with the aqueous hydrochloric acid, and in methods of treating and amalgamating the zinc.

TYPES OF COMPOUNDS REDUCED BY THE CLEMMENSEN METHOD

Aldehydes

Aliphatic Aldehydes. The conversion of heptaldehyde to n-heptane ¹⁰ in 72% yield appears to be the only recorded instance of a Clemmensen reduction of an aliphatic aldehyde.

Aromatic Aldehydes. The number of aromatic aldehydes which have been subjected to the action of zine amalgam and hydrochloric acid is not large. The original procedure of Cleramensen gives excellent results with certain placenic aldehydes but is less satisfactory for the reduction of benaddehyde. Robinson and Shah's obtained good yields from aromatic addehydes by carrying out the reaction in the presence of dilute ethanol with a succially prepared zine amalgam.

Ketones

Aliphatic and Alicyclic Ketones. Aliphatic and alicyclic ketones of low molecular weight are reduced smoothly, but those of higher molecular weight are attacked only slowly. Apparently small amounts of unsaturated compounds are formed as by-products from some ketones. Both propylene and pinaced are reported to be present in the products of the Clemmesson reduction of acetones. With ketones of the sterol scries it is necessary to employ a solvent miscible with the hydrochloric acid to increase the solubility of the carbonyl compound in the reaction mixture. This modification of procedure is not desirable with the simple aliphatic ketones, since with such compounds it favors the formation of resinous by-products.

No reduction of an aliphatic or alicyclic α -diketone has been described. The cyclic β -diketone, 5,5-dimethylcyclohexadione-1,3, undergoes reduction and rearrangement to 2.4-4-trimethylcyclopentanone-1.

$$CH_3$$
 CH_3 CH_4 CH_4 CH_5 CH_5 CH_5 CH_5 CH_5 CH_5 CH_5 CH_5 CH_5

Robinson and Shah, J. Chem. Soc., 1491 (1934).

Muller, Z. Electrochem., 33, 255 (1927).
 Dey and Linstead, J. Chem. Soc., 1063 (1935).

Several other β -diketones have been reduced without rearrangement; some of the reactions have been interrupted to produce monoketones.⁵

Aliphatic ketones containing primary, 1c secondary, 6 or tertiary 7 hydroxyl groups undergo reduction of the carbonyl group without change of the alcohol function. These observations, together with the fact that alcohols have been used satisfactorily as solvents, indicate that alcoholic hydroxyl groups are not ordinarily reduced by amalgamated zinc and hydrochloric acid. However, the direct replacement of an unactivated hydroxyl group has been observed in one case; 3-hydroxy-7,12-diketocholanic acid is reduced to cholanic acid. 8 The reduction of 1,2-glycols, which has been observed with certain sterol derivatives, 2 may depend on preliminary dehydration to ketones which then react in the usual way.

Aliphatic-Aromatic Ketones. Most aliphatic-aromatic ketones react normally, and numerous carbonyl compounds of this type, particularly phenolic ketones, have been reduced by the Clemmensen method. Cyclic ketones obtained by ring closure of γ -arylbutyric acids are also readily converted to hydrocarbons. Ketones of very slight water solubility are best reduced by employing a hydrocarbon solvent and operating in such a way that the amalgamated zinc is in contact with both the aqueous acid and the hydrocarbon solution ¹⁰ (see p. 167).

The presence of a carboxyl group attached to the aromatic nucleus frequently causes the reaction to proceed more rapidly and in excellent yields.¹¹ It is probable that the carboxyl group assists in maintaining the required concentration in the acid mixture by increasing the solubility of the carbonyl compound.

The reduction of aliphatic-aromatic ketones containing one, two, or three hydroxyl or methoxyl groups on the aromatic ring proceeds exceptionally well. Quantitative yields are obtained with the lower members, and even with the higher homologs the yields are very good. The reaction proceeds rapidly, and in some cases it is possible to employ the color produced with ferric chloride as a control test.¹²

⁵ (a) Wieland and Martz, Ber., 59, 2352 (1926); (b) Qudrat-i-Khuda, J. Chem. Soc., 206 (1930); (c) Ruzicka, Koolhaas, and Wind, Helt. Chim. Acta, 14, 1151 (1931); (d) Chuang, Ma, and Tien, Ber., 68, 1946 (1935); (e) Friedmann, J. prakt. Chem., 146, 65 (1936); (f) Bardhan and Sengupta, J. Chem. Soc., 2520 (1932).

⁶ Marker and Lawson, J. Am. Chem. Soc., 61, 852 (1939).

⁷ Lutz and Small, J. Org. Chem., 4, 220 (1939).

⁸ Borsche and Hallwass, Ber., 55, 3325 (1922).

Marker, Kamm, Oakwood, Wittle, and Lawson, J. Am. Chem. Soc., 60, 1067 (1938).
 Mikeska, Smith, and Lieber, J. Org. Chem., 2, 499 (1938).

¹¹ Cox, J. Am. Chem. Soc., 52, 352 (1930).

¹² (a) Dohme, Cox, and Miller, J. Am. Chem. Soc., 48, 1688 (1926); (b) Cox, J. Am. Chem. Soc., 52, 352 (1930).

Side reactions accompany the reduction of many alighatic-aromatic ketones, and in a few cases resinous products are formed in considerable quantities. Styrene, styrene polymers, and the pinacolone of acetophenone (formed by rearrangement of the pinacel) have been isolated as by-products in the preparation of ethylbenzene from acetophenone 13 In the reaction of 2.6-dihydroxyvalerophenone with amalgamated zinc and amirous hydrochloric acid, cleavage of the ketone has been observed. but in ethanolic solution the reduction is satisfactory.14 Although most indandiones which have been studied react normally.15 the indan produced from 2.2-diethyl-6,7,8,9-tetrahydro-1,3-a-naphthindandione by the ordinary procedure is not completely free of oxygen compounds. and reaction over an extended period yields the 2-alkyl-5.6.7,8-tetrahydronaphthalene, formed by reductive opening of the indan ring.114

Aromatic Ketones. The reduction of benzophenone and its homologs by the original Clemmensen procedure is reported to be unsatisfactory because of the formation of resineus materials. On the other hand, ahydroxybenzophenone to is transformed to p-hydroxydiphenylmethane in quantitative yield. 2.4-Dihydroxy 160 and 2.4.6-trihydroxybenzophenones 166 give the expected products in somewhat less satisfactory yields. o-Benzovlbenzoic acid is converted to o-benzylbenzoic acid, but reduction with zinc dust and alkali is more convenient and gives better yields.17 Either benzil or benzoin is transformed to diphenylethane in good yields by the action of amalgamated zine and aqueous hydrochloric acid.10 but the reduction of benzoin in the presence of ethanol affords stilbene in good yield.19 2.4,6,2',4',6'-Hexamethylbenzil is unaffected by zinc amalgam and concentrated hydrochloric acid. Anthraquinone 12 and certain of its derivatives 10 are reduced to dihydroanthracenes.

Keto Acids

α-Keto Acids. The carbonyl group of α-keto acids is attacked under the conditions of the Clemmensen reduction, but the products are the a-hydroxy derivatives rather than the completely reduced acids. For example, phenylglyoxylic acid and its ethyl ester give mandelic acid and

¹³ Steinkopf and Wolfram, Ann., 430, 113 (1923).

¹⁴ Adams, Cain, and Baker, J. Am. Chem. Soc., 52, 2201 (1940).

is (a) v. Braun, Kirschbattm, and Schuhmann, Ber., 63, 1155 (1920). (b) Fleischer and co-workers, Ber., \$3, 1255 (1920), \$6, 228 (1923), Ann., 422, 231, 272 (1921).

^{18 (}g) Klarmann, J. Am. Chem. Soc., 45, 791 (1926), (6) Klarmann and Fiedor, abid. 48, 803 (1926). If Martin, J. Am. Chem. Sec., 58, 1438 (1936).

¹⁸ Ballard and Dehn. J. Am. Chem. Soc., 54, 3969 (1932).

¹⁸ Backer, Strating, and Hussman, Rec. tran. chiss., \$5, 761 (1939).

ethyl mandelate, respectively,12 and ethyl 9-fluoreneglyoxylate yields the corresponding hydroxy ester.20

β-Keto Acids. The reduction of a few esters of β-keto acids has been investigated. Ethyl acetoacetate is transformed to ethyl butyrate in 30% yield, and ethyl benzoylacetate to ethyl hydrocinnamate in 59% yield.¹² The reduction of a β-keto ester of the bile acid series, the methyl ester of 6-ketolithobilianic acid,²¹ and of two bicyclic di-(β-keto) esters = is recorded.

 γ -Keto Acids. The most important acids of this type are those obtainable by the Friedel and Crafts reaction of succinic anhydride or its substitution products with aromatic compounds or by the action of an aryl Grignard reagent with such an anhydride. The reduction of these keto acids by one of the Clemmensen procedures is satisfactory, although in certain cases some resinification occurs. A bimolecular byproduct, the dilactone of γ,γ' -diphenyl- γ,γ' -dihydroxysuberic acid, has been isolated from β -benzoylpropionic acid.

β-Aroylpropionie acids with methoxyl groups attached to the aromatic ring are best reduced in the presence of a solvent (toluene) immiscible with the hydrochloric acid. 17 β-(4,8-Dimethoxy-1-naphthoyl)-propionic acid yields γ-(4,8-dimethoxy-1-naphthyl)-butyric acid and an abnormal product, γ-(4-methoxy-5-tetralyl)-butyric acid. The formation of the latter compound involves the reduction of the ring carrying the carbonyl group and the elimination of the methoxyl group from that ring. A side reaction in the reduction of β-(p-bromobenzoyl)-propionic acid results in the replacement of the bromine atom by a hydrogen atom. Esters of β-aroylpropionic acids undergo simultaneous reduction and hydrolysis to give γ-arylbutyric acids.

The Clemmensen reduction of purely aliphatic γ -keto acids and their esters has not been studied extensively. Ethyl levulinate ¹² yields ethyl valerate, but neither γ -ketopimelic acid nor its dimethyl ester ²⁷ is reduced.

Other Keto Acids. ô-Keto acids and molecules in which the keto group is still further removed from the carboxyl group react normally in both aliphatic and aliphatic-aromatic series. Thus, the reductions

²⁰ Wislicenus and Weitemeyer, Ann., 436, 1 (1924).

²¹ Windaus, Ann., 447, 233 (1926).

²² Guha, Ber., 72, 1359 (1939).

²³ Overbaugh, Allen, Martin, and Fieser, Org. Synthesee, 15, 64 (1935).

²⁵ Fieser and Hershberg, J. Am. Chem. Soc., 58, 2382 (1936).

²⁵ Fieser and Seligman, J. Am. Chem. Soc., 60, 170 (1938).

²⁵ (a) Fieser and Peters, J. Am. Chem. Soc., 54, 4373 (1932); (b) Haworth and Mavin J. Chem. Soc., 2720 (1932).

²⁷ Komppa, Ann. Acad. Sci. Fennicae, A51, No. 3 (1938) [C. A., 34, 2335 (1940)].

of ~(p-anisoyl)-butyric acid,** of octacesan-14-one-1,28-dioic acid ** (HO₂C(CH₂)₁₂CO(CH₂)₁₃CO,H₃, and of 22-phenyidocesan-13-one-1-oic acid ** [C₂H₃(CH₂)₂CO(CH₂)₁₁CO₂H₃ have been reported. With the last two compounds extended periods are required for the completion of the reaction.

α,β-Unsaturated Carbonyl Compounds

Little information is available concerning the Clemmensen reduction of $\alpha_i \beta_i$ -unsaturated compounds. Both the extronyl group and the ethylenic linkage of unsaturated acids of the β_i -architecture of unsaturated acids of the β_i -architecture of the β_i -architecture of β_i -architecture, but the major product from benzalacetopehenone is a bimolecular one, $1,\beta_i$ -4-tetraphenylbexane-1,6-dione. Isolated double bonds appearently are not affected by amalgamated zine and hydrochloric acid.

Chromanones are converted to chromans by means of amalgamated zine and hydrochloric acid, "a.c., 7-hydrovy-2,2-dimethylchromanone is reduced to 7-hydrovy-2,2-dimethylchroman." Acylated commarins are reduced to alkyl commarins by the method of Clemmensen," and it is reported that 6,8-diethyl-5-hydroxy-i-methylcomarnin is obtained by the reduction of 6-acetyl-8-chyl-5-hydroxy-i-methylcomarin is

The Reduction of Other Functional Groups by Amalgamated Zinc and Hydrochloric Acid

Compounds containing sensitive groups in addition to carbonyl sometimes undergo reductions of more than one type. It was mentioned above that an ethylenic link is reduced when it is conjugated with a carbonyl group. The double bond of ad-unsaturated acids, such as cinnawine said by a lase saturated by zine analezam and acid. Purpoles *and

- 15 Plant and Tombason, J. Chem. Soc., 1092 (1935).
- " Rusicks, Brugger, Seidel, and Shina, Helv Chim. Acta, 11, 496 (1928).
- 10 Hills and Robinson, J. Chem. Soc., 281 (1936)
- 31 Sengupta, J. Indian Chem Soc., 17, 183 (1940).
- Burton and Shoppee, J Chem. Soc., 567 (1939).
- Dippy and Lewis, Rec. tran. chim., \$6, 1009 (1937).

 31 (a) Bridge, Crocker, Cubin, and Robertson, J. Chem. Soc., 1530 (1937); (b) George
- ³⁰ (a) Bridge, Crocker, Cubin, and Robertson, J. Chem. Soc., 1830 (1937); (b) George and Robertson, J. Chem. Soc., 1835 (1937), (c) Anderson and Marrian, J. Biol. Chem., 127, 647 (1930).
- (a) Chowdhry and Desay Free Indian Acad. Scn. 8A, 1 (1938) [C. A., 32, 9055.
 (1938)], (b) Lumaye and Limaye, Rangamana (Suppl.) (1938) [C. A., 53, 1698 (1939)].
 (c) Desai and Elblas, Proc. Indian Acad. Scn. 8A, 567 (1938) [C. A., 53, 3356 (1939)].
- ¹⁶ (a) Wibaut and Hackmann, Rev. fran. chim., 51, 1157 (1932), (b) Wibaut and Ooster-buis, thid., 52, 941 (1933).

isoquinolines and tetrahydroisoquinolines, and in one instance (p. 160) the reduction of a naphthalene to a tetralin has been observed. The hydroxyl group of β-hydroxy acids 23 and of benzyl aleohol 12 is replaced by hydrogen upon treatment with amalgamated zinc and hydrochlorie acid. The same reagent reduces γ -aryl- γ -laetones to γ -aryl butyric acids.²⁹ The halogen of α -halo acids 40 and \alpha-haloketones 41 is substituted by hydrogen under the conditions of the Clemmensen reduction. With a few compounds the removal of a halogen atom attached to a benzene ring has been observed.55 When w-dimethylaminoacetophenone is reduced by the Clemmenson method the dimethylamino group is removed and ethylbenzene is produced.42 Somewhat similar is the formation of ethylresorcinol from 2,4dihydroxy-&-butoxyaectophenonc.43 Under certain conditions, highly reactive ketones such as 2,6-dihydroxyvalerophenone (p. 159) and 2,2diethyl-6,7,8,9-tetrahydro-1,3-naphthindandionc 15a undergo cleavage of carbon chains.

EXPERIMENTAL PROCEDURES

General Discussion

The procedure originally used by Clemmensen is satisfactory for the reduction of many carbonyl compounds which are appreciably soluble in the acid mixture or which melt below the boiling point of the reaction mixture. The exact proportions of zine and hydrochlorie acid employed are not of great importance provided that both are present in large excess. Although most reductions reported in the literature have made use of 20–40% hydrochloric acid, many have been successful with acid as dilute as 5%. It has been shown that the product obtained from β -benzoylpropionic acid in the presence of constant-boiling hydrochloric acid is not as pure as that obtained when concentrated hydrochloric acid is used.

The reduction is carried out generally by heating the mixture under reflux for a period of four to ten hours. Longer reaction periods are required in some instances. Occasionally it is desirable to carry out the

^{# (}a) Awe, Ber., 67, 836 (1934); (b) Awe and Unger, Ber., 70, 472 (1937).

²⁵ Cook and Lawson, J. Chem. Soc., 827 (1933).

²³ (a) Martin, J. Am. Chem. Soc., 58, 1438 (1936); (b) Fieser and co-workers, ibid., 58, 2382 (1936); 60, 170, 1940 (1938); 61, 862 (1939); (c) Newman and Orchin, ibid., 60, 586 (1938); (d) Hewett, J. Chem. Soc., 293 (1940).

⁴² Clemo, Haworth, and Walton, J. Chem. Soc., 2368 (1929).

^{41 (}a) Johnson and Hodge, J. Am. Chem. Soc., 35, 1014 (1913); (b) Funke and Ristic J. prakt. Chem., 145, 151 (1936).

ev. Braun and Weissbach, Ber., 62, 2416 (1929).

⁴⁴ Hurd and Fowler, J. Am. Chem. Soc., 61, 249 (1939).

The Clemmensen Reduction in the Absence of an Organic Solvent (Method I)

Reduction of β -(p-Toluyl)-propionic acid.¹⁷ A mixture of amalgamated zinc (prepared from 100 g. of mossy zinc and 5 g. of mercuric chloride as described above), 75 cc. of water, 175 cc. of concentrated hydrochloric acid, and 50 g. of β -(p-toluyl)-propionic acid is refluxed vigorously for ten hours in a 1-1. round-bottomed flask. A 50-cc. portion of concentrated hydrochloric acid is added every three hours during the heating period. After the reaction mixture has been cooled to room temperature, the solid γ -(p-tolyl)-butyric acid is collected and washed with small amounts of cold water. The filtrate and washings are combined and extracted with three 75-cc. portions of ether. The solid product is dissolved in the combined extracts and, after filtration from a small amount of insoluble material, the solution is dried over calcium chloride. The solvent is then removed and the residue is distilled under diminished pressure. The product, a colorless oil, crystallizes to a white solid melting at 61-62°. The yield is 41 g. (88%).

Reduction of 2,4-Dihydroxyacetophenone. 15, 41a, 45 A mixture of amalgamated zinc (prepared from 200 g. of mossy zinc and 10 g. of mercuric chloride as described on p. 163), 150 ec. of water, 150 ec. of concentrated hydrochloric acid, and 50 g. of 2,4-dihydroxyacetophenone (resacetophenone) is refluxed in a 1-l. round-bottomed flask until a drop of the liquid in ethanol gives no color with aqueous ferric chloride. A portion of about 10-15 ec. of concentrated hydrochloric acid is added hourly. When the color test indicates the reaction to be complete (three to four hours) the mixture is cooled and the solution is decanted from any unchanged zinc amalgam. The solution is saturated with sodium chloride and extracted with ether to remove the reaction product. Removal of the solvent yields a light yellow solid which crystallizes from benzene or chloroform as thick white prisms, m.p. 97°. The yield is 44 g. (97%).

The Clemmensen Reduction in the Presence of a Solvent Miscible with Aqueous Hydrochloric Acid (Method II)

Certain carbonyl compounds which are not appreciably soluble in the acid mixture are reduced with difficulty by Method I. In such cases the reaction is often facilitated by the addition of a solvent, such as ethanol, acetic acid, or dioxane, which is miscible with the aqueous hydrochloric acid. For example, bilianic acid is reduced by means of 2

⁴⁶ Brewster and Harris, J. Am. Chem. Soc., 52, 4866 (1930).

mixture of acetic and hydrochloric acids. and y-(3-phenanthryl)-butwic acid is obtained in 50% yield by the gradual addition of concentrated hydrochloric acid to a boiling mixture of 8-(3-phenanthroyl)propionic acid, acetic acid, and amalgamated zinc a The use of acetic acid as a solvent in the reduction of a number of natural products has become standard practice (see p. 197). In some cases it is used without the addition of hydrochloric acid.

Ethanol is employed to increase the sofubility of a-, 8-, and r-keto esters.13 It has been reported that y-keto-y-(2-fluorene)-butyric acid is unaffected by the Clemmensen reduction according to Method I, but that it is reduced almost quantitatively in the presence of aqueous ethan nol.49 The cleavage of 2.6-dihydroxyvalerophenone is avoided by carrving out the reaction in aqueous ethanol, and the reduction of other hydroxynhenyl alkyl ketones is assisted by the same solvent.50 Tho gradual addition of an ethanolic solution of the ketone or aldehyde to a refluxing mixture of aqueous hydrochloric acid and gine has given excellent yields of reduction products from various indanones " and aromatic aldehydes.2 The preparation of 4-chloro-7-methylindan illustrates this procedure.

Preparation of 4-Chloro-7-methylindan. A solution of 100 g. of a mixture of 4-chlore-7-methyl-1-indanene and 7-chlore-4-methyl-1-indanone to in 500 cc. of ethanol is added in portions, over a period of four to five hours, to a refluxing mixture of 100 ec. of water, 40 ec. of ethanol, 250 cc. of concentrated hydrochloric acid, and the amalgamated zine prepared from 350 c. of granulated zinc and 17.5 c. of mercuric chloride (see p. 163). After the addition is complete the mixture is refluxed for ten hours, during which time 200 cc. of concentrated hydrochloric acid is added in portions. The mixture is cooled; the aqueous layer is decanted and, after dilution with an equal volume of water, is extracted twice with other. The greater portion of the product is recovered by extraction of the zinc residues with other. Any lumps of material must be broken up to facilitate the extraction. The ether extracts are combined and after removal of the solvent, the residual oil is steam-distilled from an aqueous solution of sodium hydroxide. The colorless oil is separated from the distillate, and the aqueous layer is extracted with ether. The oil is combined with the ether solution and, after drying and removal of the solvent, is distilled under diminished pressure. The

⁴ Borsche and Rosenkrans, Ber., 52, 342 (1919) 4 Haworth and Mayin, J. Chem. Soc., 1012 (1933).

⁶ Koelsch, J. Am. Chem. Soc., \$5, 3885 (1933).

[&]quot;Coulthard, Marshall, and Pyman, J. Chem. Soc., 280 (1930).

⁵¹ Frener and Seligman, J. Am. Chem. Soc., \$7, 942 (1935).

If Freser and Selieman, J. Am. Chem. Soc., 53, 2482 (1936).

product is a colorless liquid b.p. 132-133°/25 mm. The yield is 88.5 g

(95%).

Reduction of γ -Keto- γ -(2-fluorene)-butyric Acid.⁴⁹ A mixture of 90 g. of γ -keto- γ -(2-fluorene)-butyrie acid, 450 cc. of ethanol, 450 cc. of concentrated hydrochloric acid, and 180 g. of amalgamated zinc is refluxed for one hour. A second 450-cc. portion of concentrated hydrochloric acid is then added, and refluxing is continued for eight hours. The mixture is cooled, and the solid is collected and dissolved by boiling with 1000 cc. of 5% aqueous sodium hydroxide. After filtration and acidification the γ -(2-fluorene)-butyric acid separates. The yield of crude product is 85 g. It is readily purified by recrystallization from acetic acid followed by recrystallization from benzene-petroleum ether, yielding white plates, m.p. 151-151.5°.

The Clemmensen Reduction in the Presence of a Solvent Immiscible with the Hydrochloric Acid (Method III)

A large number of earbonyl compounds have been reduced in poor yields by Methods I and II, and, especially in the cases of certain keto acids, the difficulty has been ascribed to the formation of insoluble polymolecular reduction products which coat the surface of the zine. The addition of a hydrocarbon solvent, such as toluene, which is immiscible with the hydrochloric acid is beneficial in those cases because it keeps most of the material out of contact with the zine, and in the aqueous layer the reduction occurs at such a high dilution that polymolecular reactions are largely inhibited.

The modification is particularly advantageous with keto acids which contain methoxyl groups. Such compounds may suffer hydrolysis of methoxyl groups during the reduction; consequently it is desirable to treat an alkaline solution of the crude reaction product with methyl sulfate, in the presence of a trace of sodium hydrosulfite if darkening occurs during methylation, to recover any demethylated material.

Certain extremely insoluble compounds cannot be reduced by this method unless both the aqueous layer and the hydrocarbon layer are in contact with the zinc.

Reduction of β-Benzoylpropionic Acid.¹⁷ To 120 g. of mossy zinc, amalgamated as described on p. 163, 75 cc. of water, 175 cc. of concentrated hydrochloric acid, and 100 cc. of toluene is added 50 g. of β-benzoylpropionic acid. The mixture is refluxed briskly for twenty-four to thirty hours, during which time a 50-cc. portion of concentrated hydrochloric acid is added every six hours. The solution is cooled to room temperature, the aqueous legarated and, after dilution with 200

cc. of water, is extracted with three 75-cc. portions of ether. The combined ether and toluene solutions are washed with a little water and dried over calcium chloide. The solvents are removed by distillation under diminished pressure, and the residue is distilled. γ -Phenylbutyric acid, b.p. 173–181 $^{\prime}$ 19 mm., is obtained as a colorless oil which solidifies to white crystals, m n. 46–48. The vield is 41 c. (90%).

Reduction of β - $\{\beta$ -Anisoyl\}-propionic Acid.¹⁷ To 120 g, of mossy zinc amalgamated as described on p. 163 are added, in the order given, the following: 75 cc, of water, 175 cc, of concentrated hydrochloric acid, 100 cc. of toluene, and 50 g, of β - $\{\beta$ -quaisoyl\}-propionic acid. The mixture is refuxed briskly for forty-eight hours, during which time a 25-cc. portion of concentrated hydrochloric acid is added every six hours. The solution is cooled to room temperature; the aqueous layer is separated and, after dilution with 200 cc. of vater, is extracted with three 75-cc. portions of other. The toluene and ether extracts are added to 300 cc. of 5% aqueous sodium hydroxide, and the solvents are removed by steam distillation.

The residual alkaline solution is cooled to 80°, and 5 to 10 ce. of methyl sulfate is added. If necessary, aqueous sodium hydrovide is introduced to keep the solution alkaline. After the mixture has been shaken or stirred for thirty to forty-five minutes, the excess alkali is neutralized and the solution is treated with charcoal. The colorless or yellow filtrate is cooled to 10° and acidified by the slow addition of hydrochloric acid. The mixture is kept in an ice bath until the precipitation of the product is complete. It is then filtered and the solid is washed with a little cold water. The crude material, obtained in quantitative yield, is sufficiently pure for most purposes. For purification it is dissolved in ether and the solution is filtered from any insoluble material. The solvent is removed and the residue is distilled under diminished pressure. The yield of \(\tau(\text{-}(\text{p-ainty})\)-butyric acid, bp. 182-180°/4 mm., mp. 01-62°, is 43 g. (94%). For further purification the acid may be recrystallized from pertodeum ether (br. 30 -60°).

Reduction of Stearophenone. Nossy nine is added to a weighed 2-L. Erlenmeyer flask until a layer about S cm. deep is formed. The weight of the zine is determined, and the metal is amalgamated by treatment with the appropriate amounts of mercoric chloride, water, and hydrochloric acid (p. 163). To the zine amalgam is added sufficient concentrated hydrochloric acid to cover about one half of it, followed by a solution of 250 g, of stearophenone in 750 ec. of xylene. The mixture is heated under reflux for seven hours, during which time gaseous hydrogen chloride is passed into the bottom of the flask to replace losses. The xylene layer is separated, the solvent renoved, and the product distifiele, bp.

220-235°/5 mm. A residue of about 30 g. of a heavy oil is discarded. The distillate is dissolved in 750 cc. of xylene and treated with another portion of zinc amalgam and hydrochloric acid as described above. The product isolated, b.p. 195-205°/4 mm., m.p. 33°, weighs 190 g. (77%). Crystallization of the *n*-octadecylbenzene from ether yields a product of m.p. 35-36°.

The Clemmensen Reduction in the Presence of Solvents of Both Types (Method IV)

Certain carbonyl compounds of very slight solubility are reduced in the presence of toluene only when a small amount of a solvent such as acetic acid, ethanol, or dioxane is added to the reaction mixture. The water-soluble solvent effects a satisfactory distribution of the compound between the two layers, permitting a low concentration of the material in the aqueous layer. 4-Hydroxy-3-phenylpropiophenone,⁵³ and 4-methyl-1-keto-1,2,3,4-tetrahydrophenanthrene ⁵⁴ have been reduced by this modification in yields of 74 and 94%, respectively. The experimental procedure is essentially the same as that of Method III.

The Clemmensen Reduction with Unamalgamated Zinc (Method V)

Unamalgamated zine has been employed successfully with eblorogenone, cholestanedione-3,6, cholestanone-7, and other ketones of the sterol family. The compound to be reduced is dissolved in 95% ethanol, and 20-mesh granulated zinc is added. To the boiling mixture small amounts of concentrated hydrochloric acid are added over a period of several hours. Apparently this procedure represents another modification suitable for ketones of very low water solubility.

TABLE OF COMPOUNDS REDUCED BY THE CLEMMENSEN METHOD

In the following pages the compounds which have been reduced by the Clemmensen procedure are tabulated. Since many of these reactions were carried out before the development of the modified procedures, it is likely that in many cases the yields reported do not represent the maxima now obtainable.

The compounds in the table are grouped according to the number of carbon atoms present. The method of reduction is indicated, and the yield is included if it is available. The nature of the product is given only when the reaction follows an abnormal course.

⁵² Harris and Pierce, J. Am. Chem. Soc., 62, 2223 (1940).

⁵⁴ Bachmann and Edgerton, J. Am. Chem. Soc., 62, 2219 (1940).

¹⁵ Marker and Rohrmann, J. Am. Chem. Soc., 61, 846, 946, 1284, 2719, 3314, 3479 (1939).

COMPOUNDS REDUCED BY THE CLEMMENSEN METHOD

C₆~C₇

Compound

			1	- Citec I
$\mathbf{C^1H^{10}G^1}$	Pentanol-1-one-4 R.P. ‡ n-Amyl alcohol	I	70	3
C'H'O'	Cyclohexadione-1.4			
Call to O.	Eth)) aretoaceists	I		3
C.H.ON	4-Methyl-5-ammoacetyhmidazole	11	30	33
C'H'O	Benzaldchyde	[]	0	418
Onto	Denzaldebyde	ī	46	1
		I	12	38
C'H'O	n-Heptanai	1	72	1
$C_1H_1O_1$	Salicy taldebyde	1	70	2
C'H'O'	m-Hydroxybenzaldehyde	1	40	2
C'II'O'	p-H3 droxybeuzaldehyde	I	95	2
C'H'O'	2.4-Dihydroxybenzaldehyde	I	_	2
	1	1 1	-	87
		l n		253
C,H,O,	2,0-Dibydrovybenzaldchyde	l ī		273
C ₇ H ₁₂ O ₅	Ethyl levulmate	11	55	33
	C ₈			
C ₅ TT ₅ O	Acetophenone	1	80	39
		1 1	60	1
CHILO	ers and trans-β-Bicyclo-0:3:3)-octanone	11	- 1	153
C'II "O	5,5-Dimethylcyclohexene-2-one-1	I	-	285
C'H'O'	p-Hydroxyscetophenone	1 1	Q	2
C ₄ H ₁₂ O ₂	5,5-Dimethylcycloheradione-1,3	1 1	- 1	182
C'H'O1	Phenylglyoxy he acid	1	70	39
	R.P ‡ Mandelie acid		- 1	
C,H,O,	3,4-Dihydroty acetophenone	1 1	75	2
C,H,O,	2,4-Dihydroxyacetophenone	1	Q	2
		1 T	al	E

82 103 O 57

5

253

I 49 390

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Ī

I 30 426

I 49 87

111 67 345

11

70 2

2,6-Dihydroxyacetophenone

2.5-Dibydroxyacetophenone

2-Hydroxy-3-methoxybenzaldehyde

2,4-Dibydroxy-5-methylbenzaldchyde

C,H,O,

C.H.O.

C'II'O'

C₄H₅O₄

Formula

^a Q_i yield reported as quantitative, Q_i yield reported as good, P_i yield reported as poor. A dash indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp 201-209

RP. reduction product

Formula	Compound	Method	Yield *	Refer-
C:H::0:	β-(Cyclopentanone-2)-propionic acid	I	72	178
		I	74	150
C'H'O'	2,4,6-Trihydroxyacetophenone	I	45	457
$C_iH_iO_i$	2,3,6-Trihydroxy-4-methylbenzaldehyde	I	_	79
$C_1H_2O_4$	2,3,4-Trihydroxyacetophenone	I	95	2
$EO_{2}H_{4}OS$	Thiochromanone	I	-	47
$C_{i}H_{1i}ON$	2-Keto-octahydropyrrocoline	I	27	250
$C_{i}H_{1}ON$	7-Keto-octahydropytrocoline	I	40	419
C ₂ H ₇ O ₂ Br	2-Hydroxy-5-bromoacetophenone	I	-	164
C.H.O.Cl	2-Hydroxy-5-chloroacetophenone	I	42	41
		I	(-	165
C ₅ H _f O ₂ Cl ₂	3,5-Dichloro-2-hydroxyacetophenone	1	; —	403
C ₂ H ₂ O ₂ B ₇	3,4-Dihydroxy-5-bromoscetophenone	I	! —	403
	R.P.1 4-Ethylresorcinol	i		i
C.H.O.CI	c-Chloro-3,4-dihydroxyacetophenone	I	G	5
	R.P. 3,4-Dihydroxyethylbenzene		1	
C _t H _t O _t Cl	2,4-Dihydroxy-5-chloroscetophenone	1	-	167
		I	_	406
C.H.O.Br.	2,4-Dihydroxy-3,5-dibromoacetophenone	I	-	103
C.H.O.Cl	2.4-Dihydroxy-3.5-dichloroscetophenone	I	<u> </u>	103
C,H,O,S	β -(α -Thenori)-propionic acid	I	72	455
	Cş	,		<u>'</u>
]	
C'H'O	Indanone-1	I	90	3
C _s H ₂₂ O	Propiophenone	I	60	1
C'H"O	Benzyl methyl ketone	I	60	1
C'H"O	m-Methylacetophenone	ī	G	19
C'H-O	p-Methylacetophenone	I	-	19
$C_3H_{14}O$	1-trans-3-hydrindanone	I		151
01110	gon: I lat . If I do a .	I		173
C'H'O	2,2-Dimethyl-3-keto-bicyclo(1:2:2)heptane	I		24
C,H;;O;	p-Methoryacetophenone	I	59	5
C ₅ H _{::} O ₅	p-Hydroxypropiophenone	I	Q	2
		П		91
C4H::O4	2 Hydroxynoxianhanana	I	73	141
C ₂ H ₂₂ O ₂	2-Hydroxypropiophenone 2-Methyl-1-hydroxyacetophenone	I	71	141
C ₄ H ₁₁ O ₂	2-Methyl-s-hydroxyacetophenone 4-Hydroxy-2,3-dimethylbenzaldehyde	I	60	73
C ₃ H ₂₂ O ₂	4-Hydroxy-2,6-dimethylbenzaldehyde	I		77
C ₅ H ₂₂ O ₂	2-Hydroxy-2,5-dimethylbenzaldehyde	I	40	75
C.H.O.	4-Hydroxy-2,6-dimethylbenzaldehyde	I	73	75 74
CHO	Date of the contraction of the c	ì	13	1=

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1

79

75

41 74

74

2-Hydroxy-3-methylacetophenone

2-Hydroxy-4-methylzcetophenone

C3H::O:

C:H::O:

^{*} Q. yield reported as quantitative; G. yield reported as good; P. yield reported as poot. A death indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209.

[#]R.P., reduction product.

Formula	Compound	Method	Yield *	Refer-
Call 10O1	4-IIydroxy-3-methylacetophenone	I		73
CallinOs	3.4-Dimethoxybenzaldehyde	Î	31	228
CallinOs	2,4-Dihydroxy-3-ethylbenzaldehyde	111	87	16I
Call 10Oa	2,4-Dihydroxy-5-ethylbenzaldehyde	II II	<u> </u>	161
CallinO.	3-Hydroxy-4-methoxyacetophenone	11		91
CaII 10Oa	2.4-Dihydroxypropiophenone	ī	60	57
CaH ₁₀ O ₃	2,4-Dihydroxy-6-methylacetophenone	ÎÎ	55	161
CaH10G1	2.6-Dihydroxy-3-methylacetophenone	III	67	312
C _a FI ₁₀ O _a	2.6-Dihydroxypropiophenone	ı i	75	390
C ₄ II ₁₀ O ₄	2.4-D:hydroxypropiophenone	ÎÎ	10	406
0111001	2,4-13-ay droxy propropactions	l i l	Q	5
C ₄ H ₁₀ O ₂	2.5-Dibydroxyproplophenone	l î l	30	426
C4119O1	\$,00Dittydroxypropiopiienone	i	30	#20 5
Call 11Oa	2.3.3-Trimethylcyclopentenc-1-one-4-car-		- 1	0
CILITIO	boxylie acid	1	!	286
	R.P.‡ 1,2,2-Trimethyl-3-cyclopentanecar- boxylic acid	١ . ١	- 1	280
CoH ₁ O ₄	3-Acetyl-2,4-dihydroxybenzaldehyde	II		339
Callada	3-Acetyl-2,6-dihydroxybenzaldehyde	ii	44	330
		''i	45	457
C ₁ H ₁₀ O ₁	2,4,6-Trihydroxyproprophenone	11		278
C:11:0:	3-Carbomethoxy-2,6-dibydroxybensaldehyde	1 1	72	246
a = a	l =	11 1	0	409
Call taOa	Dimethyl 7-ketopimelate	1 11 1	0 1	400
C ₂ H ₂ O ₄	Bicyclo(2 2 1)heptane-3,7-dione-1,2-dicar-	1 1	- 1	414
• • • •	boxylie seid	11	77	
C _t II _t OBr	4-Bromo-1-indanona	ii l		335
			77	195
C,H,OCl	4-Chloro-1-indanone	ni i	_	327
C ₁ H ₁ O ₁ B ₁	3-Bromo-6-hydroxypropiophenone	I		164
CillioiCl	3-Chloro-6-hydroxyproptophenone	I	- 1	165
C ₁ H ₂ O ₁ Cl	3-Chioro-i-methyl-6-hydroxyacetophenone	1	- 1	165
CsHsO2Cls	3,5-Dichloro-2-hydroxypropiophenone	Ī	-	408
C ₁ II ₁ O ₁ Cl	3-Chloro-4,6-dihydroxypropiophenono	I	- 1	406
C ₁ II ₁ O ₁ Br ₁	3,5-Dibromo-2,4-dihydroxypropiopherone	1 (103
C ₁ H ₁₄ ON	4-Keto-5,5'-dimethyldi-(1,2)pytrolidine	I		214
C ₁ H ₁ ON	2-Methyl-3-keto-octahydropyrrocoline	1	- 1	188
	R.P ‡ 3-Hydroxy-2-methyloctahydropyrroco- line			
C _t II ₁₀ ON	5-Methyl-7-keto-octahydropyrrocoline	1		419
CHUON	3-lieto-octahydropyridocoline	I	43	188
CallaON	4-Ketodecahydroquinolms	I	33	273
C ₁ 1I ₁₅ ON	1-Keto-octshydropyndocoline	1	60	101
		I	-	213
C ₁ H ₁₀ ON	2-Keta-actshydropyndocoline	1		213
C,11,OS	4-Ketosothiochroman	1	30	96
	R.P ‡ 1-Methylthiophthalan	_	{	
C,11,108	2,3,5-Trimethyl-4-acetothienone	I	75	95

Q. yield reported as quantitative. G. yield reported as good. P. yield reported as poor. A dashindicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp 201-209

² R.P. reduction product

C19

				,
Formula	Compound	Merhod	Yield*	Refer-
C1:H1:N2	1-Methyl-2-(3-pyridyl)-pyrrole	I	70	147
CuHuN2	1-Methyl-2-(2-pyridyl)-pyrrole	I	12	165
C_{i} : H_{i} : O	Benzalacetone	I	50	258
C: H:O	4-Ethylacetophenone	ī		19
٠,٠٠٠	22	Î	~	76
C_1 : $H_{11}O$	4-Phenyl-2-butanone	Ī	Q	1
C ₁ ·H ₁ ·O	Butyrophenone	Î	88	1
CuH ₁₂ O	2,5-Dimethylacetophenone	Î	80	11
C1:H1:O	3-Methylpropiophenone	Ī	G	19
C ₁ ,H ₁ ,O	4-Methylprophophenone	ì	65	19
$C_{11}H_{11}O$	trans-6-Decalone	Ī	60	45
C ₁₂ H ₁₄ O	cis-2-Decalone	1	~-	153
		11	75	
CriHitO	8-Methylhydrindanone-6	I		446
C _{1:} H _{1:} O	5-Methyl-2-isopropyl-bicyclo(5:1:0%)hex-	1 _ 1		~~~
0 77 0	anone-1	I	23	225
C;;H;;O	d-Thujone	I	59	235
C1:H1:O2	3-Ethyl-hydroxy-5-methylbenzeldehyde	I	60	74
C1:H::O2	5-Ethyl-4-hydroxy-2-methylbenzaldehyde	I	co	74
C2:H::O2	2-Hydrory-3,4,6-trimethylbenzaldehyde	I	-	74
C2:H2:07	3-Hydrory-2,4,6-trimethyloenzaldehyde	I	- 1	Ø
C:'H':'O'	4-Ethoryzoetophenone	I	55	5
C:.H::O:	5-Ethyl-2-bydroxyacetophenone	I	69	73
C::H::O2	2-Hydrory-2.4-dimethylacetophenone	I	6/3	73
$C_1, H_{12}O_2$	2-Hydrory-4,6-dimethylacetophenone	1	75	8
C21H12O2	2-Hydrory-4.5-dimethylacetophenone	I	76	74
$C_{23}H_{12}O_{2}$	5-Hydrory-2,4-dimethylacetophenone	I	- 1	73
$C_{1}H_{1}O_{2}$	4-Hydroxy-3.5-dimethylacetophenone	I	45	73
C::H::O:	4-Hydroxybutrophenone	1		451
	1	п	1	91
CuHuO.	2-Hydroxy-3-methylpropiophenone	I	[-1
$C_1:H_1O_2$	8-Methylbydrindione-4,6	(I)	[445
		I	- 1	155
C::H::0;	2,6-Dilydrory-3-propionylbenzeldehyde	n	}	376
$C_1:H_2:O_1$	Ethyl phenylglyoxylate	п	57	38
~ ^	R.P.‡ Eibyl mandelate	1 !	1	
$C^{zz}H^{zz}O^z$	3-Benzoylpropionic seid	m	80	495
		ш	30	455
		I	79	464
C::H::O;	y-Phanyl-y-butyrelactone	III	81	465
C_{i}, Π_{i}, O_{i}	3-Ethyl-4.6-dibydroxy-2-methylbenzaldehyde	I	64	455
C::H::O:	2,4-Dibydronytestyrophenone	1	78	57
C _{1:} H _{1:} O ₂	5-Ethyl-2,4-dibydroxyzeetophenone	1	82	85
CEO	la care	1	- 1	454
C::H::O:	2.6-Dimethoxyzoetophenone	1	-	240
$C_{11}H_{12}O_{1}$	3-Ethyl-2.4-dibydroryzcetophenone	I	1	291

Pormula	Compound	Method	Vield *	Refer-
C10H11O1	a trul			ļi
Ciolino	3-Hydroxy-4-methoxypropiophenone 2,4-Dihydroxy-3-methylpropiophenone	II		91
CulturGa	2,4-Dihydroxy-3-methylpropiophenone	1	. –	376
C16H111U1	2,4-Dihydrovyphenyl isopropyl ketone	1	71	110
C 11 0	a r Tul-ul-us lut-us	1	_	53
C10H12O1	2,5-Dibydroxybutyrophenone	I	30	426
Cullino.	2.6-Dihydroxybutyronbenona	1	75	239
CiolliaGa		1	75	390
C10111401	Cyclopentanesparocyclopentan-2-one-5- carboxylic acid			400
CtoH1sOs	4-Keto-5-eyelopentylvalerie neid	1 1		438
CioHiaOa	(1.6-Dimethyleyelohexanone-3)-acetic acid	I	_	441
CialliaO4	1,3-Diacetyl-4,6-dihydroxybenzene	I	82	329
CiallinO4	1/2-Diffeet21-4/0-district Abenzeue		84	86 54
C16H16O4	6-2-Hydroxybenzoylpromonie acad	1 1	= 1	452
C1611 10O4	p-3-11ydroxy benzoyipropionie acid	III		
	1		96	403
0 77 0	0.10 702	I	-	432
C16H11O4	2.4.0-Trimethorybenzaldehyde	I		111
C14H11O4	5-Ethyl-2,3,4-Trihydroxyacetophenoue	I	75	194
Ctall 10O4	2-Hydroxy-1-(β-hydroxyethoxy) acetophenone	I		
C16H11O4	2,4,6-Trihydroxybutyrophenone	I	56	457 80
Ciellino,	3-Carboxy-1-hydroxypropiophenona	I		
C10II 14O4	3-Acetyl-2,6-dihydroxyacetophenona	I	46	291
C1eHteO4	3-Carboxy-2.5-dimethoxybensaldehyda	11	- 1	278
C10H14O3	3-Carboxy-3-methylcyclopentanone-2-β- propuonic acid	1	- 4	412
C16H1OBr	4-Bromo-7-methyl-1-andanone	II I	87	175
C ₁₆ H ₁ OBr	7-Bromo-i-methyl-1-mdanone	ii	87	175
CitiioCl	4-Chloro-7-methyl-1-indanone	II	92	222
ClaII OCI	7-Chloro-4-methyl-1-manone	II I	05	222
CioII OCI	4-Chloro-6-meths I-1-indanona	ii ii	78	395
CipitinOtBr	5-Brome-2-hydroxybutyrophenona	'z	13	104
CiallinOaCl	5-Chloro-3-ethyl-2 hydroxyacetophenona	i	= 1	41
ChillinoiCl	5-Chloro-2-hydroxy-4-methylpropiophenone	î	= 1	165
CloH trOrCl	5-Chloro-2 hydroxybutyraphenano	i	= 1	165
Ciell 10OcCl	3.5-Dichloro-2-hydroxybutyrophenono	i	= 1	408
CtoH O.Br	8-4-Bromobenzoylpropionie scid	mi	75	263
CallaOct	5-Chloro-2,4-dabydroxs butyrophenono	i [79	169
Cigitation	Or Charles at a cond party to partitions	i		167
C10H11ON	-Dunethylaminoscetophenoso	î l	1	96
Cignificat	R.P.1 Ethylbenzene	- 1	- 1	
C ₁₀ H ₁₀ ON	Ethyl (3,5-dimethyl-2-pyridyl) ketone	1	- 1	299
Ollariford	R P.1 Ethyl (3,5-dimethyl-2-pyridyl) carbinol	- (
C ₁₀ H ₁₇ ON	1-Keto-2-methyloctahydropyridocolina	1		250
CiaHirON	1. Keto-S-methylociahydropyridocolma	1	74	273
C ₁₀ H ₁₁ OS	2.7-Dimethyl-3-keto-3,4,5,6-tetrahydro-β-	1.0	1	
	thionaphthen	1		287
C ₁₀ H ₁₂ O ₂ S	8.(2,5-Dimethyl-3-thenoyt)-propionic acid	r	71	287

Q, yield reported as quantitative, G, yield reported as good, P, yield reported as poor. A dash
indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209

RP., reduction product.

C11

Formula	Compound	Method	Yield*	Refer- ence †
C ₁₁ H ₁₂ O	4.7-Dimethyl-1-indanone	I	73	458
C ₁₁ H ₁₂ O	7-Methyl-1-tetralone	1	44	35
C ₁₁ H ₁₂ O	Benzocyeloheptenone-1	I	40	27
C ₁₁ H ₁₄ O	2.4.6-Trimethylacetophenone	Ī	G	19
CHILITO	2,1,0-11methylacotophonole	Ī	74	319
C11H14O	2,4,5-Trimethylacetophenone	Ī	77	319
		I	G	19
$C_{11}H_{14}O$	2,4-Dimethylpropiophenone	I	50	386
$C_{11}H_{14}O$	Isovalerophenone	I	-	428
$C_{11}H_{14}O$	n-Valerophenone	I	58	471
$C_{11}H_{16}O$	9-Methyl $\Delta^{4.10}$ (or $\Delta^{5.10}$) octalone-1	1	98	206
$C_{11}H_{16}O$	[2,2-Dimethylbicyelo(2:2:13.6)heptyl]-	1	1	
	acetaldehyde	I	77	24
$C_{11}H_{15}O$	Dicyclopentyl ketone	I	ļ —	217
C11H20O	Cyclohexyl n-butyl ketone	I	 -	217
C11H20O	Cyclohexyl isobutyl ketone	I	 -	217
C11H22O	Methyl nonyl ketone	I	-	46
		I	88	1
$C_{11}H_{22}O$	3-n-Butylheptanone-2	I	16	46
C11H22O	Caprone	I	73	46
C11H12O2	5,6-Dimethoxy-1-indanone	III	<u> </u>	458
C11H12O2	6-Methoxytetralone-1	I	_	432
C11H12O2	Ethyl einnamate	11	82	38
	R.P.‡ Ethyl hydrocinnamate	1		ļ
C11H14O2	4-Hydroxy-2-methyl-5-isopropylbenzalde-	1	ł	1
	hyde	I	87	2
$C_{11}H_{14}O_{2}$	4-Ethoxypropiophenone	I	77	5
$C_{11}H_{14}O_2$	2-Hydroxy-5-n-propylacetophenone	I	l —	106
C11H14O2	5-Ethyl-2-hydroxy-3-methylaeetophenone	I	65	73
C11H14O2	5-Ethyl-2-hydroxy-4-methylaeetophenone	l I	60	73
C11H14O2	3-Ethyl-2-hydroxy-5-methylaeetophenone	I	1 -	73
C11H14O2	4-Ethyl-5-hydroxy-2-methylaeetophenone	I	61	60
C11H14O2	2-Hydroxy-3,4,5-trimethylacetophenone	I	75	74
C11H14O2	2-Hydroxy-3,5,6-trimethylacetophenone	I	75	74
C11H14O2	4-Hydroxy-3,5-dimethylpropiophenone	I	50	106
$C_{11}H_{14}O_{2}$	4-Hydroxyphenyl isobutyl ketone	I	-	428
C11H14O2	2-Hydroxy-3-methylbutyrophenone	II	-	91
$C_{11}H_{14}O_2$	2-Hydroxy-5-methylbutyrophenone	II	-	91
$C_{11}H_{14}O_{2}$	4-Hydroxy-3-methylbutyrophenone	I	57	106
		II	 -	91
$C_{11}H_{14}O_{2}$	2-Hydroxy-4-methylbutyrophenone	II) —	91
C11H14O2	4-Hydroxyvalerophenone	II	-	91
C11H14O2	Endomethylene-1,4-5,8-diketodecalin	I	59	72
$C_{11}H_{16}O_{2}$	9-Methyl-2,4-diketodecalin	I	60	114

^{*} Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209.

[#] R.P., reduction product.

Formula	Compound	Method	Yield *	Refer-
C11H16O1	1,8,8-Trimethylbicyclo(1:2:3) octane-2,4-dione 3-Carboxy-1-keto-1,2,3,4-tetrshydronaphtha-	I		90
	lene	1	J	61
CuHuO ₄	β-3-Methylbenzoylpropionic acid	m	84	200
C11H11O1	β-p-Totuylpropionic acid	1	80	35
		ĺī	80	135
	į.	111	9.3	200
C11H12O1	Ethyl benzoylacetate	11	59	38
C11H11O1	7-Benzoyl-n-butyrie acid	1		230
C11H11O1	α-Methyl-β-benzoylpropionic acid	1 1		35
Callagos	7-Hydroxy-2,2-dimethylehromanone-4	1 1	60	251
C11H14O1	3,5-Diethyl-2,6-dibydroxybenzaldebyde	1	60	455
Cull ₁₄ O ₂	2,6-Diracthoxypropiophenone	1	~ !	240
CulluOs	3,5-Diraethoxy propiophenone	I		31
CuH ₁₄ O ₄	3,4-Dimethoxypropiophenone	I	65	5
CnH ₁₄ O ₂	4,5-Dimethoxy-2-methylacetophenone	1	78	228
Cull 4O2	4. Hydroxy-3-methoxybutyrophenone	11	!	91
CuH ₁₄ O ₂	2,6-Dib) droxyphenyl n-butyl ketone	11	73	396
CuHHO.	2.6-Dihydroxyphenyl isobutył Letone	II	73	226
CuHuO,	2.4-Dihydroxyphenyl isobutyl ketone	I	83	110
		I	-	53
CuH ₁₄ O ₁	2,4-Dihydroxyphenyl n-butyl ketone	I	~	53
	1	I	85	396
CuHuO:	3-Ethyl-1,6-dshydroxy-2-methylacetophenone	1	64	433
CuH ₁₁ O ₁	2.4-Dihydroxy-3-methylbutyrophenone	I		376
CuHuO,	2,5-Dimethoxypropiophenone	i	54	5 280
CuH ₁₄ O ₁	0471 1 11 11 11 11 11	i	IS I	203
Cultuo	2.5-Dihydroxyphens 1 m-buts 1 Letone	i	30	426
CHILIO	2,5-Dihydroxyphenyl isobutyl Letone	i		239
Cull 10	2,5-Dihydroxy-3,4,6-trimethylacetophenone	nî	_ 1	315
CulluO4	B-m-Angoy Ipropionie seid	III	en i	465
- III	p rangegapt options action	r	15	467
		ī	67	207
CuH ₁₂ O ₄	β-p-Anlaoy lpropionie acid	ш	90	475
-11-22-04	,	III	85	465
		I		452
		1	~	432
		1	~-	284
		1	=	163
	1	1	1	35
C11H11O4	α-Methyl β-2-hydroxy benxoy lpropsonic acid	I	~]	437
C11H11O4	3 Carboxy-4-bydroxybuts rophenone	1		59
CnHnO.	5,7-Dihydroxy-2,3-dimethylehromanone-4	11		227
CuHnO ₄	3.Acetyl-4-ethyl-2,6-dshydroxybenraldehyde	11		339
C"H"O"	2,4,6-Truncthoxyacetophenone	1	23	111

^{*}Q, yield reported as quantitative, G, yield reported as good, P, yield reported as poor. A dash

indicates that the yield is not reported

† Reference numbers refer to the bibliography on pp. 201-209

‡ R.P., reduction product.

Formula	Compound	Method	Yield*	Refer- ence †
C11H14O4	2,4,6-Trihydroxyphenyl n-butyl ketone	I	25	457
	2,4,6-Trihydroxyphenyl isobutyl ketone	n	63	341
C ₁₁ H ₁₄ O ₄	4-Carboxy-1,3-diketodecalin	ī		114
C11H14O4	4-Bromo-2,7-dimethyl-1-indanone	l ii	87	232
C ₁₁ H ₁₁ OBr	1	II	87	232
C ₁₁ H ₁₁ OBr	7-Bromo-2,4-dimethyl-1-indanone	II	80	266
C ₁₁ H ₁₁ OBr	4-Bromo-7-ethyl-1-indanone	п	80	266
C ₁₁ H ₁₁ OBr	7-Bromo-1-ethyl-1-indanone	I	50	419
$C_{11}H_{15}ON$	5-Isopropyl-7-keto-octahydropyrrocoline		30	164
C ₁₁ H ₁₂ O ₂ Br	5-Bromo-2-hydroxyphenyl n-butyl ketone	Į	_	165
$C_{11}H_{13}O_2Cl$	5-Chloro-2-hydroxyphenyl n-butyl ketone	I	_	40S
$C_{11}H_{12}O_2Cl_2$	3,5-Dichloro-2-hydroxyphenyl n-butyl ketone	I	1	133
$C_{11}H_{12}O_{2}N$	Ethyl β-2-pyridoylpropionate	I	63	1
C11H12O2N	β-3,5-Dimethyl-2-pyridoylpropionic acid	I	91	299
	C ₁₂	<u>i</u>		
				261
C12H14	Di-Δ¹-cyclopentenylacetylene	I	5	201
	R.P. 1,2,3,3a,4,5,6,7,8,8b-Decahydro-as-		ļ	i
0	indacene	1		1
$C_{12}H_{10}O$	Methyl α-naphthyl ketone	I	55	1
		I		126
C12H10O	Methyl β-naphthyl ketone	III	52	292
		III	52	220
		I	_	113
$C_{12}H_{12}O$	2,3-Benzobicyelo(0:3:3)-2-octen-4-one	I	-	442
C12H14O	7-Ethyl-1-tetralone	[I	_	35
$C_{12}H_{14}O$	6-Acetyl-1-tetralin	I	-	22
$C_{12}H_{14}O$	6,7-Dimethyl-1-tetralone	I	80	135
C12H14O	5,7-Dimethyl-1-tetralone	I	SO	135
		I	_	35
C12H14O	5,8-Dimethyl-1-tetralone	I	80	135
C12H14O	2,4-Dimethyl-1-tetralone	I	77	393
C12H14O	2,2-Dimethyl-1-tetralone	I	81	306
C12H16O	4-Ethyl-2,5-dimethylacetophenone	I	83	14
$C_{12}H_{16}O$	p-n-Propylpropiophenone	1	_	76
$C_{12}H_{16}O$	3-Methyl-1-phenylpentanone-1	I	38	236
C12H16O	n-Caprophenone	I	56	471
C1:H::O	Cyclohexyl cyclopentyl ketone	1	_	217
C1:H::O	S.10-Dimethyl-2-ketodecalin	I	-	115
C1:H::O	Cyclododecanone	I	76	99
$C_{12}H_6O_2$	7,8-Diketoacenaphthene	I	35	172
C TT A	2-Acetyl-1-naphthol	I	60	176
$C_{12}H_{10}O_{2}$				
		I	-	415
C ₁₂ H ₁₀ O ₂ C ₁₂ H ₁₀ O ₂ C ₁₂ H ₁₀ O ₂	4-Acetyl-1-naphthol 5-Methoxy-4,7-dimethyl-1-indanone	I I II		415 416 458

^{*} Q. yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209.

[;] R.P., reduction product.

		,	γ	
Formula .	Compound	Method	Yield *	Refer-
CullinOs	7-Methoxy-2-methyi-1-tetralone	I	59	437
Culling	3.5-Diethyl-2-hydroxyacetophenone	l î	60	73
Culling	5-Ethyl-4-methoxy-2-methylacetophenone	l î	75	73
CulluO	3-Ethyl-2-hydroxy-4.5-dimethylacetophenone	l i	66	73
CullinDe	4-Ethyl-2-hydroxy-3,5-damethylacetophenone) i	72	73
CulluOs	2-Hydroxy-5-n-propylproprophenous	Ì	70	141
Culling	4-Hydroxy-3-n-propylpropsophenone	Ī	70	141
Cull nO	5-Ethyl-2-hydroxy-3-methylproptophenons	i	51	106
CultuOs	3-Ethyl-4-bydroxy-5-methylpropiophenone	î	29	106
CulluOs	4-Hydroxy-3,5-dimethy ibutyrophenons	ìi	48	106
CulluO	2-11ydroxy-3-methylphenyl a-butyl ketone	1I		91
Culling	2-Hydroxy-5-methylphenyl n-butyl ketone	II	_	91
C11H14O2	2-Hydroxy-4-methylphenyl a-butyl ketone	H	_	91
CulluO	4-Hydroxy-3-methylphenyl m-butyl ketone	ii	_	91
CulluO	4-Hydroxyeaprophenone	ii		91
CulluOz	2,4-Diketo-5,9-dimethyldecalin	Ιï	_	114
CuH 11O	1.11-Ethynylenebiscyclopentanol	i i	3	261
Culling	7-(p-Tokyi)-buten-3-ore acid	i	Q	378
CitititO	2-Phenyleyelopentanone-3-carboxylic acid	i		442
CuH ₁₁ O ₂	3.4 Dihydroxy-1.2-benzocycloheptenone-1'-			-10
012111104	methylene ether	1	!	27
C12II14O2	β-4-Ethylbensoylpropionic acid	111	91	397
0.0.00	p-141m/ (pento) (propromo acre	III	94	339
	1	ī	- 1	219
		ī		35
CuffuO.	a,a-Dimethyl-fi-beasoylpropionic acid	ī	71	306
- 1111-1		ī	_	283
CulliaO.	Ethyl 8-bensoylpropionate	1	- 1	36
CulluO.	8-2,5-Dimethylbenzoylpropionie acid	ī	90	116
		I	80	135
C1111101	β-2,4-Dimethylbensoylpropionic acid	1	80	135
- 1311		1		35
C1.H1.O.	5-3.4-Dimethylbensoylpropionic acid	İ	80	135
CiaHiaOa	3-Acetyl-2-hydroxy-4,6-dimethylacetophenons	Ī	60	8
Culli4O1	6.7-Dimethoxy-1-tetralone	1	70	154
		I	77	122
CıallısO	3,5-Diethyl-2,6-dshydroxy-4-methylbenzalde-	- }	J	
	hyde	1	-	455
C11H11O	4-Hydroxy-3-methoxyphenyl n-butyl ketone	1	- 1	118
	1	11	= 1	91
CulluO	2,4-Dihydroxyphenyl n-amyl ketone	1	85	53
		1	84	110
Cullu0 ₁	2,4-Dihydroxyphenyl monmyl ketone	I	82	53
	North and the state of	i	30	426
C12H11O4	2,5-Dihydroxyphenyl isosmyl ketone	7		426 239
	1	*)	- }	-00

Q. yield reported as quantitative, G, yield reported as good; P, yield reported as poor. A dash industes that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp 201-209

IRP reduction product

Formula	Сотроилд	Method	Yield *	Refer- ence †
C ₁₂ H ₁₆ O ₂	2-Hydroxy-5-methoxyphenyl n-butyl ketone	I	51	280
C12H15O3	3-Carboxy-2-(3-mcthylspirocyclohexane)-	1	[ĺ
	cyclopentanone-1	I		429
C12H10O4	8-Acetyl-7-hydroxy-4-methylcoumarin	I		424
C12H14O4	α-Methyl-β-p-anisoylpropionic acid	I	86	437
C12H14O4	β-4-Mcthoxy-2-methylbenzoylpropionic acid	1		284
C12H14O4	β-2-Methoxy-5-methylbenzoylpropionic acid	I	-	284
C12H14O4	β-3-Methoxy-2-methylbenzoylpropionic acid	11	ł	290
C12H14O4	β-3-Methoxy-4-methylbenzoylpropionic acid	ш	86	465
C12H14O4	β-4-Methoxy-3-methylbenzoylpropionic acid	I		284
C12H14O4	ô-2-Hydroxybenzoylvaleric acid	ш	97	403
C ₁₂ H ₁₄ O ₄	2,4-Dihydroxy-5-propionylpropiophenone	I		54
C ₁₂ H ₁₄ O ₄	5-Hydroxy-6,7-dimethoxy-1-tetralone	Ī		432
C ₁₂ H ₁₄ O ₄	5-Hydroxy-7-methoxy-2,2-dimethyl-	1 -		
012111404	chromanone-4	11	48	252
C12H14O4	7-Hydroxy-5-methoxy-2,2-dimethyl		~	
Cimitot	chromanone-4	n		252
C12H16O4	2,4,6-Trihydroxyphenyl n-amyl ketone	ī	54	457
CIMITO	2,1,0-11mydroxyphenyi n-amyi metone	Î	70	56
C12H16O4	3,4,5-Trimethoxypropiophenone	ī	31	112
C12H16O4	ω-Butoxy-2,4-dihydroxyacetophenone	Î		318
OBILIO	R.P.: Ethyl resorcinol	1		020
C12H14O5	β-2.5-Dimethoxybenzoylpropionic acid	m	42	403
C12H14O5	β-2,4-Dimethoxybenzoylpropionic acid	I		432
C ₁₂ H ₁₄ O ₅	β-3,4-Dimethoxybenzoylpropionic acid	m	62	465
01211103	p o, 2 Dimotholy college, proproduce	I		452
		Î		122
C1:H1:O6	β-2-Hydroxy-3,4-dimethoxybenzoylpropionic	1 -		
01,111,00	acid	I		432
$C_{12}H_{12}O_6$	3,5-Diacetyl-2,4,6-trihydroxyacetophenone	Î		54
C12H5ON	4-Benzoylpyridine	Î	80	61
C ₁₂ H ₁₂ OBr	4-Bromo-7-isopropyl-1-indanone	II I	87	317
C12H12OBr	7-Bromo-1-isopropyl-1-indanone	п	87	317
C12H15O2Br	5-Bromo-2-hydroxyphenyl n-amyl ketone	Ī		164
C12H15O2Cl	5-Chloro-2-hydroxyphenyl n-amyl ketone	Ī		165
C12H15O2Cl	3-Chloro-6-hydroxy-2-methyl-5-isopropylace-	1		
	tophenone	1		165
C12H15O2CI	5-Chloro-2,4-dihydroxyphenyl n-amyl ketone	п	-	167
	C ₁₃			
C12H15O	6,7-Benzo-1-indanone	I	53	139
$C_{12}H_{15}O$	Benzophenone	Î		38
C12H12O	1-Acetyl-4-methylnaphthalene	Ī		425
Clantico	1 -1ccty 1-1-memy maphenatene			

 $^{^*}$ Q. yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209.

[‡] R.P., reduction product.

Formula	Compound	Method	Yield *	Refer ence
C11H11O	2-Acetyl-6-methylnaphtbalene	II	_	333
Ciallino	6,7-Cyclopenteno-I-tetralone	11	89	233
		1		433
Cultuo	3-Keto-1,2,3,4,10,11-hexabydrofinorene	1		435
$C_{11}H_{14}O$	1,2,3,10-Tetrahydroperinaphthanone-7	i i	_	48
CulluO	6-Acetyl-7-methyltetralin	1 11	77	383
CulluO	2-Ethyl-5-methyl-1-tetralone	1	59	92
C ₁₃ H ₁₄ O	3-Ethyl-5-methyl-1-tetralone	1 1	43	92
CialliaO	4-Ethyl-7-methyl-1-tetralone	1 i 1	86	149
CuHuO	7-Ethyl-3-methyl-1-tetralone	i		197
C11H10	2,2,7-Trimethyl-1-tetralone	i	53	306
C ₁₃ H ₁₀ O	2,3,5-Trimethyl-1-tetralone	ı i l	Q	102
Cultuo	Phenyl n-hexyl ketone	î	53	471
CaHaO	Cyclohexyl 2-methylcyclopents I ketone	ÎÎ	33	217
Cullino	Cyclotridecanone	i		227
CiaII 10Oa	p-Hydroxybenzophenone	î	0	3
C ₁₃ H ₁₃ O ₃	2-Propionyl-1-naphthol	i	50	176
CuHuO ₁	9-Keto-7,8,9,12-tetrahydrodibenzopyran	i	0	436
Ciallia01		i	75	
CHAINO	2,2-Diethyl-audan-1,3-done	Î	58	13
CuHuO:	2 Tab. 3 2 to 3 to 3 to 3 to 3 to 3 to 3 to 3	ni		337
	5-Ethyl-7-hydroxy-S-methyl-(†)-tetralone	I I	65	385
C'1 <u>II</u> 15O	6-Methoxy-4,7-dimethyl-1-tetralone	i	76	458
C"II"O	7-Methoxy-5,8-dimethyl-1-tetralone	i	20	474
C12H14O2 C12H14O2	Discrylmentilene	î	20	73
	4,5-Diethyl-2-hydroxy-3-methylacetophenone	1 1	64	73
CPH 11O	3,4-Dirthyl-2-hydroxy-5-methylacetophenone	i 1	50	73
C'II''O'	5-Ethyl-1-methoxy-2,3-dimethylacetophenone	î	49	106
Ciallito	3-Ethyl-1-hydroxy-5-methylbutyrophenone	11	93	91
C11H11O1	2-Hydroxy-3-methylphenyl n-amyl ketone	ii		91
C11H14O1	4-Hydroxy-3-methylphenyl s-amyl ketono	ii		91
CistinOs	2-Hydroxy-5-methylphenyl mamyl ketone	11	-	91
C14H14O4	2-Hydroxy-1-methylphenyl n-amyl ketone	11	= 1	91
Ctall 13O2	2-Hydroxyphenyl n-hexyl ketone	n	= III	91
CaHtaOs	4-Hydroxyphenyl n-hexyl ketone	ï		115
C11H10O1	7-Acetyl-1-keto-10-methyl decalin	î		261
C14H20O1	1,1'-Ethynyleyclobexanolcyclopentanol R.P.‡ 3a,4,4a,5,7,8,9,9b-octahydro-a-naph- thindsn	Î	١,	201
C11H10O1	3-Ethyl-2,4-diketo-9 methyldecaliu	1	- 1	114
C12H1O2	7,8-Dikelo-1-methoxyacenaphthens	ī		172
C ₁₃ H ₁₀ O ₂	2,4-Dihydroxybensophenona	ī	30	55
CzaHzaOz	8-5-Indanoylproptome acid	TIL		233
O38174O3	μ-υ-γιασιασγησυριστια acou	ī		133
C. H. O.	B-(1-Keto-3-tetralyl)propsonic acid	ĭ	70	63
C12H14O2 C11H14O1	5-p-Anisyt-cyclohexane-1,3-dione	I		11
CaHaOs	Ethyl a-methyl \$-bensoylpropionate	I	- 1	36
CnH ₁₁ O ₁	β,β-Dimethyl-y-bennylbutyne acid	I	- 5	30

· Q, yield reported as quantitative, G, yield reported as good, P, yield reported as poor. A dash

indicates that the yield is not reported † Reference numbers refer to the bibliography on pp 201-202

² R P . reduction product.

Formula	Compound	Method	Yield*	Refer- ence †
C12H16O2	α,α-Dimethyl-β-p-toluylpropionic acid	I	82	306
C12H16O2	Ethyl β-o-toluylpropionate	II	43	179
C12H16O2	Ethyl β -p-toluylpropionate	I		36
C12H16O2	β-4-Isopropylbenzoylpropionic acid	Ī	80	135
- •• •	6,7-Dimethoxy-2-methyl-1-tetralone	Î	64	134
C ₁₂ H ₁₆ O ₂	0,1-Dimethoxy-2-methy1-1-tetraione	Î	-	129
C12H16O2	6,7-Dimethoxy-3-methyl-1-tetralone	I	64	134
C12H15O2	2,6-Dimethoxyphenyl isobutyl ketone	I	43	140
C12H15O2	2,5-Dimethoxyphenyl isobutyl ketone	I	48	280
C12H15O2	4-Hydroxy-3-methoxyphenyl n-amyl ketone	II		91
C12H15O2	2,4-Dihydroxyphenyl n-hexyl ketone	I	 —	53
C12H16O4	2,4,6-Trihydroxybenzophenone	I	50	56
C12H12O4	8-Acetyl-7-methoxy-4-methylcoumarin	II		274
C12H12O4	7-Hydroxy-4-methyl-8-propionylcoumarin	1		424
C12H12O4	5-Hydroxy-4-methyl-6-propionylcoumarin	II	l	340
C12H16O4	3-Carboxy-4-hydroxyphenyl isoamyl ketone	ī		89
C12H16O4	3-Carboxy-4-hydroxy-n-caprophenone	Î	88	89
C12H16O4	β-4-Methoxy-2,5-dimethylbenzoylpropionic	1		
Opposition	acid	I	92	94
C12H16O4	α-Methyl-β-3-methoxy-2-methylbenzoylpro-	(1	
	pionic acid	II	-	225
C12H16O4	ō-p-Anisoylvaleric acid	I	73	183
$C_{12}H_{16}O_4$	5-Hydroxy-6,7-dimethoxy-2-methyl-1-tct-	l		
	ralone	I		437
C12H15O4	2,4,6-Trihydroxyphenyl n-hexyl ketone	I	30	457
$C_{12}H_{16}O_{5}$	α-Methyl-β-3,4-dimethoxybenzoylpropionic			
	acid	I	45	129
		I	_	134
$C_{12}H_{15}O_{5}$	β-Methyl-β-3,4-dimethoxybenzoylpropionic	,	}	1
	acid	Į I		134
$C_{12}H_{15}O_{5}$	γ-3,4-Dimethylbenzoylbutyric acid	I	73	448
$C_{12}H_{16}O_6$	α-Methyl-β-2-hydroxy-3,4-dimethoxybenzoyl-	1	1	ĺ
	propionic acid	I	_	437
$C_{12}H_7OBr$	2-, 3-, or 4-Bromofluorenone-9	II	Q	196
$C_{12}H_{2}OBr$	o-Bromobenzophenone	I	 	351
		I	50	88
C12H2OBr	4-Bromo-5,6-benzo-1-indanone	I	<u> </u>	33
C12H15OBr	4-Bromo-7-1-butyl-1-indanone	II	70	264
C ₁₂ H ₁₅ OBr	7-Bromo-4-1-butyl-1-indanone	II	70	264
C12H17O2CI	5-Chloro-2-hydroxyphenyl n-hexyl ketone	I	一	165
$C_{12}H_{17}O_{1}C_{1}$	5-Chloro-2,4-dihydroxyphenyl n-hexyl ketone	II	1 —	167
$C_{12}H_{15}ON$	1-Keto-5,6-benzo-1,2,3,4,7,8-hexahydro-	1	}	
0 77 037	pyridocoline	I	37	276
C12H21ON	1-Keto-5,6-benzododecahydropyridocoline	I	52	276
$C_{12}H_{11}O_{2}N$	β-2-Quinolylpropionic acid	I		244
$C_{12}H_{12}O_{2}N$	Ethyl β -(3,5-dimethylpyridoyl-2) propionate	I	91	299

^{*} Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209.

² R.P., reduction product.

C14

Formula	Compound	Method	Yield *	Refer-
CHHHO	1- and 4-Keto-1,2,3,4-tetrshydrophenanthrene	IV	69	371
CHHIO	S-Methyl-peri-naphthanone-7	liv	70	394
C14HHO	3-Acetylacenaphthene	l i		20
C14H14O	1-a-Naphthylbutanone-1	Î	_	33
C14H14O	1-β-Naphthylbutanone-1	Ιi.	-	33
C ₁ H ₁₄ O	1-Acetyl-4-ethylnaphthalene	i i i	70	126
CuHuO	2-(4-Methyl-1-naphthyl)propanol-2	ì		425
CuHuO	I-Keto-1,2,3,4,5.6,7,8-oetahydrosnthracene	1 i 1		35
CHHHO	9-Keto-I,2,3,4,9,10,11,12-octahydrophenan- threne (cir and trans momers)		_ /	331
C14H14O	ω-Cyclohexenylacetophenone R.P.‡ β-Phenylethylcyclohexene	ıî	43	335
Ct*H12O	4,7-Dimethyl-3-teopropyl-1-indanone	1	- 1	344
Cielliio	2,2-Diethyl-1-tetralone	1	63	306
C14H14O	5-Methyl-8-isopropyl-1-tetralone	i i	52	37
Cullino	6-Acetyl-7-ethyltetralin	iii	1	22
CuHuO	o-Phenylacetophenone	I	66	174
C14II10O	9-Ketododecabydrophenanihrene (m p. 94°)	ī	86	336
CuHnO	9-Ketododecahydrophenanthrene (m p. 51")	ī	88	\$36
Callao	9-Ketododecabydrophenanthrene	ī	81	201
CuHuO	9-Ketotetradecabydrophenanthrene (m p. 48°)	7 /	Q	336
CuH ₁₁ O	trans-3-Methyl-1-propyl-1,2,4a,5,6,7,3,8a- octabydro-1-paphthalenone	11	62	360
CuHuO	2-Acetyl-8,30-dimethyldecalin	ï	- 1	115
CuHuO	Cyclotetradecanona	î	87	99
Ctall'4Os	Anthraquinone	î		3
-14-14-1	R.P.2 Dihydro- and hexahydroanthracene	• 1	- 1	
C14H11O1	Bensil	1	Q	3
Ctall taOa	Benzoin	i	84	3
141111111111111111111111111111111111111	a-canonia	rî	50	119
C12H14O4	4-Hydroxy-3-phenylacetophenone	īv	70	393
CLIII4O	2.4-Diketo-1,2,3,4,9,10,11,12-octahydro-	~ 1	1	400
	phenanthrene	1	35	470
C14H14O4	2-n-Butyroyl-1-hydroxynaphthalene	i l		176
C14H14O1	2.2-Diethyl-4-methybrdan-1,3-dione	i	29	25
CuHuO	2,2-Diethyl-5-methylindan-1,3-dione	ī	73	25
CraHraOr	7-Hydroxy-9-keto-1,2,3,4,9,10,11,12-octahy-	- 1	. 1	
21411101	drophenauthrene	111	63	331
C14H18O1	5-Ethyl-7-methoxy-8-methyl-1-tetralone	1	70 :	337
C ₁₄ H ₁₄ O ₁	S-Ethyl-7-methoxy-5-methyl-1-tetralons	ī		337
C14H14O1	6-Methoxy-3,4,5-trimethyl-1-tetralone	i		225
H ₁₅ O ₁	3.5-Diethyl-2-methoxy-6-methylacetophenone	1	43	73
C14Ha ₀ O ₂	2-Hydroxy-4-methylphenyl a-hexyl ketone	n l	1	91
CaH mOs	3-Ethyl-2,4-diketo-5,9-dimethyldecalin	1	- 1	114

^{*} Q, yield reported as quantitative; G, yield reported as good, P, yield reported as poor A dash indicates that the yield is not reported.

† Reference numbers refer to the bibliography on pp. 201-209

² R.P., reduction product.

Formula	Compound	Method	Yield *	Refer-
C14H11ON C14H11ON C14H12ON C14H12ON C14H12OS	2-Acetylianthanole 3-Acetylianthanole 3-Acetylianthanole 5-Phenyl-7-ketogoethydropyrrocoline 6-Acetylhennylydrocarbusole Phenacyl phenyl sulfide R.P.‡ (a-Methylhennyl)phenyl sulfide	111 11 1	16 32 20	155 155 419 212 96

C15

C14I1110	Benzalacetophenone	1		285
	R.P.‡ Tetrsphenylhexadione			
$C_{11}\Pi_{11}O$	2-Ethyl-4,5-benzo-1-indanone	1	~	33
Ct.HHO	1-Keto-2-methyl-1,2,3,4-tetrahydrophe-	1		
	nanthrene	(I	Name of	121
C11H11O	1-Keto-4-methyl-1,2,3,4-tetrahydrophe- nanthrene	ıv	94	897
CiaII id	1-Keto-9-methyl-1,2,3,4-tetrahydrophe-		1	1
	nanthrene	1	J	132
Callao	4-Keto-3-methyl-1,2,3,4-tetrahydrophe-	í -		200
	nanthrene	lτ		121
CaHaO	4-Keto-7-methyl-1,2,3,4-tetrahydrophe-	-	i	1
	nanthrene	ı		125
CaHaO	8-Ethylperinsphthanone-7	ī	64	33
CallaO	1-Keto-3,4,5,6,12,13-hexahydro-peribenso-	_		"
- 1010-	acensphthene	I	1 -	65
CaH toO	a-Keto-octahydromethylenephenanthrene	Ī	70	65
Callao	6.7-Cyclopenteno-1-keto-2.2-dimethyl-1.2.3.4-		,	
	tetrahydronanhthalene	1	l -	433
CuHuO	7-Methyl-1-keto-1,2,3,4-tetrahydronaphtha-			
	lene-2,2-spirocyclopentane	I	-	410
CulluO	1-Keto-1,2,3,4-tetramphthalene-2,2-spiro-		1	
	cyclohexane	I	-	249
CullinO	Acetyldiethylmesitylene	1	45	474
CullerO	Phenyl n-octyl ketone	2	51	471
CuHuO	4a,5,6,7,8,8a Hexahydro-3-a-propyl-4-ethyl-			
	1(2)-naphthalenona	I	54	259
C14I114O2	4-II ydroxy-3,5-dunethylbenzophenore	1	40	106
C14H14O2	4-Hydroxy-3-phenylproptophenone	IV	74	398
H ₁₄ O ₂	4.5-Cyclohexenyl-2,2-dimethylindan-1,3-dione	1	70	26
		1	~	22
CtaH11O2	1-Hydroxy-2-naphthyl n-butyl ketone	3	50	178
CtellarOs	2-Hydroxy-3,5-di-n-propylpropiophenone	1	71	141
C23H22O2	2-Hydroxy-3,5-dimethylphenyl n-hexyl ketono	1	60	106
C14H2:O2	4-Hydroxy-3,5-dimethylphenyl n-hexyl ketone	1	53	106

^{*} Q. yield reported as quantitative, G. yield reported as good, P. yield reported as poor. A dash indicates that the yield is not reported

IRP, reduction product.

[†] Reference numbers refer to the bibliography on pp 201-209

Formula	Compound	Method	Yield *	Refer- ence †
C ₁₅ H ₂₆ O ₂	1-(1-Cyclohexanol)-3-n-propyl-1-hexyne-3-ol R.P.‡ 1,2,4a,5,6,7,8,8a-Octahydro-3-n-propyl-	I	6	259
C15H25O2	4-ethylnaphthalene Dihydrocalameone	I	l	413
C ₁₅ H ₁₀ O ₂	1,4-Diketo-3-phenylisochroman	Ī	l	304
C15111003	R.P.‡ Dibenzyl-o-carboxylic acid	•	1	ł
C15H14O2	2,4-Dihydroxy-3-methylphenyl benzyl ketone	I	-	376
C15H14O2	α-Methyl-β-1-naphthoylpropionic acid	I		121
C15H14O3	α-Methyl-8-2-naphthoylpropionic acid	I	75	121
C15H14O:	β-Methyl-β-2-naphthoylpropionic acid	I		150
C15H14O2	β-5-Methyl-1-naphthoylpropionic acid	11	90	150
C15H14O2	β-8-Methyl-2-naphthoylpropionic acid	I	-	163
C15H14O2	β-Phenylpropionylresorcinol	I	_	53
	1	I	50	54
C15H15O2	1-Phenacylcyclopentane-1 acetic acid	I		230
C15H15O2	α,α-Dimethyl-β-5-indanoylpropionic acid	I	-	433
C15H15O2	α,α-3-Methylcyclopentane-β-benzoylpropionic			
	acid	I	ì —	283
C15H15O2	α,α-Cyclopentane-β-(p-toluyl)-propionic acid	I	-	410
C15H15O2	α,α-Cyclohexane-β-benzoylpropionic acid	I	 	248
		I	<u> </u>	283
C15H22O2	2,4-Dihydroxyphenyl n-octyl ketone	I	 	53
C15H21O1	Tetrahydrosantonin	I	53	100
		I	l —	103
		I	G	158
$C_{15}H_{12}O_4$	2,6-Dihydroxy-3-(phenylacetyl)-benzalde-	_	j	0
	hyde	I	-	376
C15H14O4	β-Phenyl-2,4,6-trihydroxypropiophenone	I	1 =	51
$C_{15}H_{14}O_4$	β-4-Methoxy-1-naphthoylpropionic acid	IV	60	402 242
C H O	0.735-4	I	-	334
$C_{1i}H_{1i}O_{i}$	β-5-Methoxy-1-naphthoylpropionic acid	п	58	254
CHO	#23Yeth 0 343 1 1 1 1	ш	51 62	298
$C_{Ii}H_{Ii}O_{i}$	β-3-Methoxy-2-naphthoyl propionic acid	III	02	301
C15H14O4	6-Acetyl-7-hydroxycyclohexeno-(1',2',3,4)-	111	_	501
Cimitot	coumarin	I	l '	311
C15H15O4	α-1-Keto-7-methoxy-5,8-dimethyl-1,2,3,4-	1	_	011
Cimilion	tetrahydronaphthyl-2-acctic acid	I	75	94
C15H22O4	Humulinic acid	II.	38	50
C13H24O4	Dihydrohumulinic acid	II	- 1	50
$C_{13}H_{16}O_{3}$	5-2,5-Dimethylbenzoyl-5-hydroxybutane-	-		
	β,γ-dicarboxylic acid lactone	1		107
$C_{13}H_{15}O_{3}$	5-2,5-Dimethylbenzoylhutane-β,γ-dicarboxylic	_	1	
	acid	1	39	107
$C_{15}H_{27}O_6$	Diethyl bicyclo(3:2:2)nonadionedicar-			
	boxylate	IV	-	349

^{*} Q. yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-222.

[#] R.P., reduction product,

Formula	Compound	Method	Yield *	Refer-
C ₁₄ 1I ₁₀ O ₄ C1	Ethyl a-chlory \$64-methoxy-2,5-dimethyl- benzoglyropionate R.P.2 7-4-3lethoxy-2,5-dimethylphenylbutyric acid	1	_	94
	C ₁₆			
Cullino	4-Neto-1.2.3.4-tetrahydrofluoranthene	1	70	80

Cidlino	4-Keto-1,2-3,4-tetrahy-frofluoranthene	1	70	80
CHILLO	2-Acetylphenanthrene	ī	16	138
	1	1	t0	142
C14H11O	3-Acetylphenanthrene	1		138
	1	1	10	142
Ciellie0	3-Phenyl-1-tetralone	1	1 -	67
		1	-	t56
C ₁₄ H ₁₄ O	7-Phenyl-1-tetralone	III	1 -	383
C14I114O	I'-Methyl-3'-keto-2,3-cyclopentenoscenaph-		1	1
	thene	17.	85	356
C14H14O	3-o-Tolyi-1-indanone	I	G	68
CHILLO	3-p-Tolyt-1-indepens	1	0	68
Chall 10	1-lieto-as-hexahydropyrene	IV.	65	404
C14II11O	1. Keto-1,2,3,4-tetrahydro-8,9-seephenanthrene	1	P	476
CitHitO	3-Acctyl-1-ethyl-acenaphthene	1	-	20
C14II14O	9-Acetyl-1,2,3,4-Tetrahydrophenanthrene	IV	88	371
CHILHO	1-Keto-2,2-dimethyl-1,2,3,4-tetrahydro-		,	7
	phenanthrene	1	70	343
CittiiO	1-Keto-2,9-dimethyl-1,2,3,4-tetrahydro-		,	
	phenanthrene	1	-	150
C,EI,O	1-Keto-4.S-dimethyl-1,2,3,4-tetrahydro-		Į	
	phenanthrene	1	-	150
Ctilito	4-Keto, 1,7-dimethyl-1,2,3,4-tetrahydro-		ļ	l
	phenanthrene	1		125
C14H14O	4-Neto-3,7-demethyl-1,2,3,4-tetrahydro-	t	1	150
	phenanthrene	1	_	150
ChHHO	4-Keto-3,3-damethyl-1,2,3,4-tetrahydro-	1	73	343
	phenanthreno	1	13	343
$C_{14}H_{16}O$	4-Keto-5,7-damethyl-1,2,3,4-tetrahydro- phenanthrene	1		150
	1-Keto-devalvedropyrene	Ť		65
C14II1sO	2-Methyl-2-(2'.4'-Dumethylphenyl)-Attetra-		-	0.5
CiellaoO	hydrobensaldebado	I	Sı	202
Cullad	7-Ethyl-1-keto-1,2,3,4-tetrahydronaphthalene-	•		-0-
Clerran	2.2 spirocyclopentane	1		410
Cullao	1-Keto-7-methyl-1,2,3,4-tetrahy dronaph-	-		-10
CITTINO	thelene-2.3-sparocyelohecane	1		248

Q. yield reported as quantistare, G. yield reported as good, P. yield reported as poor. A dust indicates that the yield is not reported.

[†] Reference numbers refer to the hibbography on pp. 201-209

R.P , reduction product.

			ī
Formula Compound	Method	Yield*	Refe ence
C16H20 5-Acetyl-6,7-diethyl-1,2,3,4-tetrahydro-			22
naphthalene	I I	_	99
C ₁ :H ₂ :O Cyclohexadecanone			51
C ₁₆ H ₂ O Muscon (β-methylcyclopentadecanone)	I		0.1
C _{1t} H ₁₂ O ₂ 7-Keto-7,8,9,10-tetrahydrobenzo(b)- naphtho(2,3-d)furan	11	10	353
C _{1t} H _{1t} O ₂ 4-Keto-7-methory-1-methyl-1,2,3,4-tetra- hydrophenanthrene	I	_	191
C12H12O2 4-Keto-7-methoxy-S-methyl-1,2,3,4-tetra- hydrophenanthrene	I	37	190
C _{1t} H ₂ :O ₂ 1,4.5,8-Di-(endomethylene)-9,10-diketo- tetradecahydroanthracene	I	36	72
C ₁₂ H ₂₄ O ₂ 3-Ethyl-4-hydroxy-5-methylphenyl <i>n</i> -hexyl ketone	I	<i>5</i> 3	106
C15H25O2 Cyclohexadecan-1,9-dione	I		82
C1:H1:O2 4,4'-Diacetyldiphenyl ether	I	_	310
C ₁₀ H ₁₄ O ₂ β-1-Acenaphthoylpropionic acid	I	60	476
C ₁₀ H ₁₄ O ₂ β-3-Acenaphthoylpropionic acid	IV	50	465
C ₁₂ H ₁₄ O ₂ β-4-Phenylbenzoylpropionic acid	I III	0	476 382
	II	_	381
C ₁₂ H ₁₄ O ₂ α-Phenyl-β-benzoylpropionic acid	III	7 6	307 322
C ₁₆ H ₁₆ O ₂ β-Phenyl-β-benzoylpropionic acid	I	- 1	230
C ₁ ·H ₁ ·O ₂ α,α-Dimethyl-β-1-naphthoylpropionic acid	I	49	343
C _{1c} H _{1c} O ₂ α,α-Dimethyl-β-2-naphthoylpropionic acid	I	55	343
C ₁ ·H ₁ ·O ₂ β-1-Ethyl-1-naphthoylpropionic acid	IV	94	371
C ₁₂ H ₁₅ O ₂ α-Ethyl-β-1-naphthoylpropionic acid	1	-	150
C ₁₆ H ₁₆ O ₂ Methyl β-1-methyl-1-naphthoylpropionate	I	88	132
C _{1c} H _{1c} O ₂ β-6,7-Dimethyl-2-naphthoylpropionic acid	I	90	150
C _{1c} H _{1c} O ₂ α-Methyl-β-4-methyl-1-naphthoylpropionic acid	I	75	150
C ₁₂ H ₁₂ O ₂ α-Methyl-β-5-methyl-1-naphthoylpropionic acid	I		132
C _{1ε} H _{1ε} O ₂ α-Methyl-β-6-methyl-2-naphthoylpropionic acid	I	70	150
C ₁₆ H ₁₆ O ₂ β-Methyl-β-6-methyl-2-naphthoylpropionic			150
acid	1		230
C ₁ H ₂ O ₂ 1-Phenacylcyclohexane-1-acetic acid	I		200
C ₁ H _± O ₁ α,α-3-Methylcyclopentane-β-p-toluylpropionic acid	I	-	283
α_{i} α_{j} α_{j	I		410
C ₁ (H _± O ₂ α,α-Spirocyclohexane-β-p-toluylpropionic acid	1		248
C:tH _Ξ O: γ-1-Keto-7-ethyl-1,2,3,4-tetrahydronaphthyl- 2-n-butyric acid	IV	85	397

^{*} Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A da indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209.

[‡] R.P., reduction product.

	,			-
Formula	Compound	Method	Yield *	Refer
CuffmO4	α.α-Cyclopentano-β-4-ethylbenzoylpropionic	1		
CiellinOs	a.a.Cyclohexane-3-p-tohydpropionic seid	1 1	_	410
Culling	2,4-Dihydroxyphenyl n-nonyl ketone	ı i	=	248
CullaO	6-2-Ketocyrlopents lunders he acid	i	= 1	53 439
Culling	8-2-Dibanzofurov Invenionie acid	mi	S3	364
CtsH1001	Anison	111	72	397
CullinOs	8-4-Methoxy-6-methyl-1-naphthoylpropponic	,	12	331
(14111904	acid	1	50	116
C14H14O4	A-0-Methoxy-5-methyl-2-naphthoylpropions			
Cullia0a	G-Acetyl-7-hydroxy-5'-methylcyclobezeno-	1	53	190
Citerian	1'2'43-coumana	1 1	- 1	311
C1eH1eO1	G-Acetyl-7-hydroxy-4'-methylcyclohexeno-	Ι'Ι	- 1	3
	1',2',4,3-coumarin	ı	- 1	311
C14H toO4	a-1-Keto-7-methoxy-5,8-dimethyl-1,2,3,4-	1 - 1	- 1	
	tetrahydronaphths 1-2 propionie acid	1 1	84	94
C14II14O4	&2.6-Dimethoxy-1-naphthoylpropionic acid	ni i	54	221
CHII10	8-4.8-Dimethoxy-1-naphthoxlpropionic acid	IV	25	221
		11	20	255
C14H14O4	\$-4. Methoxy-2,5-dimethylbenzoylbutane-\$,7-	1	1	
	dicarbox; he anhydride	1 [80	93
C14H14O4	3-4-Methoxy-2,5-dimethylbenzoyl-3-bydroxy-	1 }	- 1	
	butane-\$,y-dicarboxylic acid lactone	1	83	107
C14IT40O4	\$4. Methoxy. 2,5-dimethylbenzoylbutane-\$,7~			
	dieschoxy he seid	1	53	94
CIATIO.	7-4. Methoxy-2,5-dimethylbenzos ipropune-			
	α,α,β-trientboxylie acid	1	84	91
C14H11049	3.6-Discets iphenox three	1	- 1	310
C14II 10O1SCI	3,6-bes-(Chlorosretyl)-phenoxthine	1	- 1	310
	C ₁₇			
				253
Culluo	1'-Keto-1,2-eyelopentenophenanthrene	11	_	
CtrHtaO	3'-Keto-1,2-cyclopentenophenanthrene	IV IV		258 258
C11H12O	3'-Keto-3,4-cyclopentenophenanthrens 1'-Keto-9,10-cyclopentenophenanthrens			258 271
Cullino	1'-Keto-9,10-cyclopentenophenanthreno 5,6-Benzo-1,2-dibydro-3-benzonaphthenone	I		271 258
C11H1O	2.Propionylphenanthrene	ıv [235 369
C ₁₇ II ₁₄ O	2.Propionylphenanthrene 3.Propionylphenanthrene	iv		369
CuH ₁₄ O CuH ₁₄ O	1-Acetyl-4-methylphenanthrene	rv		397
CuH ₁₁ O	3-Acetyl-4-methylphenanthrens	177		397
CHILLO	3-Acetyt-o-metayipitenancinens	1		

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4'. Keto-1',2',3',4'-tetrabydro-2,3-benzo-

fluorene

CuHuO

Q, yield reported as quantitative, Q, yield reported as good, P, yield reported as poor. A dish indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp 201-209

^{\$} R.P , reduction product.

Formula	Compound	Method	Yield*	Refer- ence †
C17H14O	1'-Keto-1,2-cyclopenteno-9,10-dihydro- phenanthrene	17.	_	295
C ₁₇ H ₁₄ O	3'-Keto-3,4-dihydro-1,2-cyclopenteno- phenanthrene	11	-	215
C ₁₇ H ₁₄ O	3'-Keto-1,2-cyclopenteno-9,10-dihydro- phenanthrene	IV	-	295
C ₁₇ H ₁₄ O	1-Keto-2,3-cyclopenteno-1,4-dihydro- phenanthrene	1	55	421
C1:H1:0	4-Keto-2,3-cyclopenteno-1,4-dihydro- phenanthrene	1	-	249
		I	55	421 332
C ₁₇ H ₁₄ O	2,3-Diphenylcyclopentene-2-one-1 R.P.‡ 1,2-Diphenylcyclopentane	I	_	
C1:H1:O	2,3-Diphenylcyclopentanone-1 (cis)	III	54 —	305 332
C17H110	2,3-Diphenylcyclopentanone-1 (trans)	III	66	305 332
C1:H1tO	?-Isobutyrylfiuorene	I	-	15
C1:H110	2-Benzyltetralone-1	I	-	64
C17H110	4-Methyl-3-phenyltetralone-1	I	 -	156
$C_{17}H_{16}O$	1-Keto-2,3-cyclopentano-1,2,3,4-tetrahydro-	1	72	297
C T 0	phenanthrene	I	76	3
C17H12O C17H12O	1,5-Diphenylpentanone-3 1-Keto-2,2,9-trimethyl-1,2,3,4-tetrahydro-	1	10	
Clinio	phenanthrene	I	70	343
C17H15O	1-Ethyl-4-keto-7-methyl-1,2,3,4-tetrahydro-			
	phenanthrene	I	Q	131
C ₁₇ H ₁₁ O	4-Keto-1,2,7-trimethyl-1,2,3,4-tetrahydro- phenanthrene	ı	_	124
C1:H1:O	4-Keto-1,3,7-trimethyl-1,2,3,4-tetrahydro-	1	1	
	phenanthrene	I	-	124
$C_{17}H_{15}O$	4-Keto-1,6,7-trimethyl-1,2,3,4-tetrahydro-	1		
0.77.0	phenanthrene	I	-	124
$C_{17}H_{22}O$	3-Keto-1,2-cyclopentano-3,4,9,10,11,12-hexa- hydrophenanthrene	I	1_	209
C1:H2:0	1-Keto-6,7-cyclopenteno-1,2,3,4-tetrahydro-	1		-35
	naphthalene-2,2-spirocyclopentane	I	l —	421
		I	1 —	249
C17H22O	7-Ethyl-1-keto-1,2,3,4-tetrahydronaphthalene- 2,2-spirocyclohexane	I	_	248
C17H210	42,5,6,7,82-Hexahydro-3-n-butyl-4-n-propyl-	1	1	
	1(2)-naphthalenone	I	57	259
$C_{17}H_{22}O$	Civetone	I	_	81
C17H15O2	1-Methyi-2-(6-methorynaphthyi-2)-cyclo-			1
C17H1102	pentanone-5 4-Keto-7-methory-1,2-dimethyl-1,2,3,4-tetrz-	m	_	373
-,,,	hydrophenanthrene	I	55	152

^{*}Q. yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dad indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209.

^{\$} R.P., reduction product.

Formula	Compound	Method	Yield •	Refer-
C11H11O1	2,2-Dimethyltetrahydroacenaphth-a, \$\beta\$-indan-			i —
	I,3-dione	1	92	26
CHHMO:	2,2-Drethyltetrahydronaphth-a, B indan-1,3-			
	dione		-	26
		I	~	23
CuHmOa	2,2-Diethyltetrahydronaphth-3,6-indan-1,3-		~	21
Christian 1	dione	ı .	45	26
	4.50	î		22
CnHzO2	2.2.5-Triethyl-4.7-dimethylandan-1.3-dione	ī	81	12
Culling,	2,2-Diethyl-4-methyl-7-tsopropylindan-1,3-	-		•
	dione	1	76	25
C17H14O4	1-(a-Naphthoyl)-A'-cyclopentene-2-carboxylic			
	neid	I	-	421
	I	1 1	- 1	249
C111114O3	1-(\$-Naphthoyl)-A'-cyclopentene-3-carboxylie	1		
	#dd	1 1	~-]	249 431
C ₁₇ H ₁₄ O ₁	4-Keto-1-phenyl-1,2,3,4-tetrahy-dronaphthose	٠ ۱	~	477
Chrittol	and	111	78	193
C ₁₂ H ₁₄ O ₂	8-2-Fluoroylpropionie acid	11	ă l	143
CuH ₁₄ O ₄	Ethyl 9-fluoreytformate	ï	80	43
	R.P.: Fluorenbydroxyacetic acid	- 1		
CuH ₁₆ O ₂	S-Acetyl-+keto-7-methoxy-1,2,3,4-tetrahydro-		- 1	
	phenanthrene	_ I }	- 1	122
C17H14O2	Methyl 8-3-acenaphthoylpropionate	111	60	465
0.17.0	1 to North and and an area of an about to	1 }	47	476
CuH ₁₄ O ₁	1-(a-Naphthoyi)-cyclopentane-2-carbox; lic		79	297
CuHuOs	1.3-Di-p-anisylpropanone-1	mi	81	357
Cirling	8-6-1 ropropy i-2-naphthoylpropionic acid	ī	60	150
CuH ₁₀ O ₂	7-2 Naphthyl-a. B. T-trimethylbutyrolactons	111	87	377
CtrH2004	a,a-Spirocyclopentane-3-(5-indanoyl)-	i	- 1	
	propionie acid	1]	- 1	421
		I	- [249
CuH _m O ₃	a,a-Cyclohexane-S-(p-ethylbensoyl)-proptome		- 1	248
	acid 2.4-Dihydroxyphenyl n-decyl ketone	i	(248 53
Cull NO	7.4'-Dimethoxy-2,3-dihydrosoffavone	11	24	350
CuH ₁₀ O ₄ CuH ₁₀ O ₄	Homopteroearpin	m	1	350
CirHigOS	2.6-Diphens lpenthranone	1	40	97

^{*} Q, yield reported as quantitative, Q, yield reported as good P, yield reported as poor A dash indicates that the yield is not reported

[†] Reference numbers refer to the bebliography on pp. 201-209.

f R.P., reduction product.

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Formula	Compound	Method	Yield*	Refer- ence †
C11H14O	1'-Keto-3'-methyl-1,2-cyclopentenophenan-			
	threne	I	_	144
$C_{11}H_{14}O$	4-Keto-1,2,3,4-tetrahydrochrysene	IV	60	359
		I	91	135
$C_{13}H_{14}O$	1-Keto-1,2,3,4-tetrahydro-5,6-benzanthracene	I	l —	138
C::H::0	1'-Keto-1',2',3',4'-tetrahydro-3,4-benzphenan-			
	threne	77	71	404
$C_{i}H_{i}O$	4-Keto-1,2,3,4-tetrahydrotriphenylene	II	71	295
$C_{11}H_{11}O$	cis-6-Keto-5,6,11,12,13,14-hexahydrochrysene	I	55	397
C11H110	3-Ketoherahydrochrysene	IV	! —	345
C::H::0	c-Cyclohexenyl-1-acetylnaphthalene	11	42	335
$C_{i}H_{i}O$	2-y-Phenylpropyl-1-indenone	I	_	67
C2:H2:O	1-Keto-1,2,3,4-tetrahydrophenanthrene-2,2-		}	1
	spirocyclopentane	I	ì —	241
		I	 	117
$C_{11}H_{11}O$	1-Keto-1,2.3,4.9,10,11,12-octahydro-		i	
	triphenylene	IV	74	371
C::H::O	2-Keto-1,2,3,4,5,6,7,8,13,14,15,16-codemby-	({
	drochrysene	m :		205
$C_{2}H_{2}O$	4-Ketododecahydrotriphenylene	I	_	270
C25H25O	417.11-Herademhydrochrysenone-6	IV	60	700
$C_{23}H_{22}O$	A12-Heradembydro-1,2-benzanthrone-3	IV	47	450
$C_{23}H_{23}O$	Laurophenone	I	_	440
		I	47	471
C11H14O2	1-Benzoyl-4-methoxynaphthalene	IV	2 0	455
C21H21O2	2,2-Dimethyl-a-finorenindan-1,3-dione	I	-	15
C15H16O2	trans-2,11-Diketo-1,2,9,10,11,18-hembydro-	1		
	chrysane	I	75	135
C::H::O:	cis-2,11-Dileto-1,2,9,10,11.18-heralydro-	-		
	chrysene	Ţ	70	135
$C_{13}H_{14}O_{2}$	rsc-2.11-Diketo-1,2,9,10,11,18-kembydro-			į
	chirace	; I	-	117
C11H11O2	3-Desory-11-heto-quilenin	. II		355
	R.P. Desoxyequilenin	* ±	i	
$C_{1i}H_{2i}O_{2}$	3-Descry-11-hetoequilenin	7	_	355
0 77 0	R.P.; Monohetolesonyequilenin	-	į	ra p
$C_{12}H_{14}O_{2}$	7-Methory-3'-keto-3,4-tilhydro-feydopenteno-	`		345
CuHarO:	1'2':12-phenanthrene,	1 IV	: 83	395
CHE-O.	4-Hydrory-3-planyl-n-exprophenone Oestrone	IV	60	145
Cimen) Oslobe	II	62	145
CaH=O:	1,1'-Ethynylenstetrahydronaphthologelo-	п	;	1
	herard	Ī	b	251
	R.P. 1.22c.3.45.65c.7.8-Demiyorous	1 1	-	1

Formula	Compound	Method	Yield *	Refer ence
C ₁₈ H ₁₂ O ₁	Cyclooctadecan-1,10-drone	1		82
C11H11O1	8-2-Anthroylpropionic acid	IV.	70	445
C15H16O1	β-2-Phenanthroylpropionio acid	H	50	138
Cullio.	β-3-Phenanthroylpropionic acid	11	50	138
CnH ₁₄ O ₁	β-9-Phenanthroylpropionic acid	111	79	365
C15H15O1	β [2-(9.10-Dihydrophenanthroyl)]-propionic	(l		
	acid	IV	92	369
		ıv	85	295
CnH ₁₁ O ₁	3-Keto-2,5-dinhenvievelopentane-1-carboxylic	1 1	11	
	acid			83
C15H14O1	o-(6-Tetroyl) benzoic acid	lii	83	39
CaHaO4	a,a-Spirocyclopeniane-8-1-nophthoylpro-	1 1		
	propie acid	ı	- 1	417
		l i l	- I	241
CullinO.	a. B-Dimethyl-a-phenyl-B-benzos lpropionic	- 1	- 1	
	acid	IV	80	401
CaHaOs	β [9-(1,2,3,4-Tetrahydrophenanthroyi)-pro-			
	monic acid	IV	98	371
C11H10O1	1,4-Di-p-anisylbutanone-i	III	53	387
C1sH10O1	8-6-4-Butyl-2-naphthoylpropionic acid	IV	78	465
CuH ₁₀ O ₁	8-5.6.7.8-Tetramethyl-2-paphthoylpropionic	- 1		
	acid	m		377
CullinOs	Methyl a,a-dimethyl-8-4-methyl-1-naphthoyl-		- 1	
*11	propionate	1	44	343
Culling	β [9-(1,2,3,4,5,6,7,8-octahydrophenanthroyi)]-	- 1		
-11	propionie acid	1	- 1	270
C11H11O1	8-[6-(1,2,3,4,9,10,11,12-octahydrophenan-			
	throyi)]-propionie seid	1	- I	331
CullinOr	\$-(5 or 6)-Cycloherane-1-spirobydriadoylpro-	1		
	plonic acid	1	- 1	331
CulluOs	2,4-Dihydroxyphenyl n-undecyl ketone	1	(1)	53
		1		54
C14II 10O4	Methyl β-4-methoxy-4'-xcnoylpropionate	1		216
CnH ₁₁ O ₄	Methyl β-4-methoxy-3-xenoylpropionate	1	58	216
CHH204	1.5-Di-n-caprovl-2.4-dihydraxybenzeno	I	- 1	54
CnHnO.	a Phenyl-5-3,4-dimethoxybenzoylpropionic	- 1	- 1	
	acid	1		187
C15H12ON	2-Phenyl-5-benzoylpyridma	1	0	40
C ₁₂ H ₂₁ O ₂ N	D:hydrocode;nono	1	- 1	29
C,H,O,N	Dihydrohydroxyeodeinona	1	- 1	71
		1	42 3	368
	R.P ‡ Dihydrobydrovythebanone			
C14H14O4N	Dihydrothebanone	I	- 1	71

^{*} Q, yield reported as quantitative; Q, yield reported as good, P, yield reported as poor A dish indicates that the yield is not reported

[†] Reference numbers refer to the bibliography on pp 201-209 ‡ R.P., reduction product.

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Formula	Compound	Method	Yield*	Refer- ence †
C15H14O	4,5-Methylene-7-keto-7,8,9,10-tetrahydro-			001
	ehrysene	IV	59	391
C15H14O	4,5-Methylene-10-keto-7,8,9,10-tetrahydro- ehrysene	IV	41	391
$C_{15}H_{16}O$	1'-Methyl-5-keto-5,6,7,8-tetrahydro-1,2-		85	399
	benzanthracene	IV	83	369
$C_{11}H_{11}O$	2-Methyl-4-keto-1,2,3,4-tetrahydrochrysene	IV		399
$C_{15}H_{15}O$	1-Keto-1,2,3,4-tetrahydro-11-methylchrysene	IV.	85	365
$C_{13}H_{12}O$	2-Methyl-1-keto-1,2,3,4-tetrahydrotriphenylene		77	
C15H2::0	Methyl \$-9-fluorenyl-\$-methyl-n-propyl ketone	I	-	255
C13H22O	1-Keto-9-methyl-1,2,3,4-tetrahydrophenan-		1	
	threne-2,2-spirocyelopentane	I	 -	417
		I		241
C15H2=0	2-Keto-10-methyl-2,3,4,5,6,7,8,9,10,11-		Ì	1
Citatio	decahydrochrysene	I	1 —	279
C19H2O	4-Keto-1-ethyl-7-isopropyl-1,2,3,4-tetrahydro-		1	
Churo	phenanthrene	I	Q	131
C15H21O	Androstenone	I	40	342
C ₁₅ H ₂₁ O	Methyl n-heptadecyl ketone	I	Q	1
	Lactone of 2-(\alpha-hydroxy-o-methylbenzyl)-1-	_		1
$C_{1i}H_{1i}O_2$	naphthoic acid	п	38	220
0.77.0	Lactone of 2-(\alpha-hydroxy-\alpha-methylbenzyl)-1-	1	1	1
C13H14O2	naphthoie acid	11	74	220
0 11 0	2,2-Diethyl-5-cyclohexenylindan-1,3-dione	ī	GS	26
C13H2:O2		1	1 00	1
C15H22O2	2,2-Diethyltetrahydroacenaphtho-α,β-indan- 1,3-dione	I	62	26
	1,5-010119	I	1 -	22
0.77.0	0	п		145
C15H24O2	Oestrone methyl ether	111	1	1
C13H24O2	2,2-Diethyltetrabydronaphtho-α,β-indan-	I	74	34
0.77.0	1,3-dione	III	35	224
C13H21O2	Androstan-3,17-dione	111	33	1
C15H14O2	β-(4,5-Methylene-1-phenanthroyl)-propionic acid	IV	55	391
G T O	•	IV	57	329
C15H16O2	β-4-Methyl-1-phenanthroylpropionic acid	IV	85	399
$C_{15}H_{12}O_{2}$	β-5-Methyl-3-phenanthroylpropionic acid	IV	50	399
$C_{15}H_{16}O_{2}$	β-Methyl-β-2-phenanthroylpropionic acid	•	77	365
C13H14O2	a-Methyl-3-9-phenanthroylpropionic acid	III	1 "	1 0,00
$C_{13}H_{14}O_{3}$	β-(4,5-Methylene-2,10-dihydro-2-phenan- throyl)-propionic acid	IV	44	391
CTO		11	2.7	1 022
$C_{13}H_{17}O_{2}$	a.a-Spirocyclopentane-3-14-methyl-1-naph-		1	417
C14H22O2	thoyl)-propionie acid 1,5-Di-p-anisylpentan-3-one	III	63	357
CuH2O1	Androstan-3,17-dion-2-ol	I	64	224
C::H::O:		I	"	53
Chural	2,4-Dihydroxyphenyl n-dodecyl ketone	į 1	1	, ,

^{*}Q. yield reported as quantitative; G, yield reported as rood; P, yield reported as poor. A dash indicates that the yield is not reported.

I Reference numbers refer to the biblingraphy on pp. 201-209.

² R.P., reduction product.

Formula	Compound	Method	Yield *	Refer-
C14H20O4	6-Acetyl-7-hydroxy-frans-octalino-(2',3',4,3)-			_
	coumarin	1		311
C ₁₄ H ₁₇ ON	Methyl-S-phenyl-I-keto-2-(benzo-5,7-indoledi-			
	bydnde-2,8)	r	95	69
	R.P ‡ 1-Methyl-2-naphthylacetic acid	- 1		03
CuH22O4N	Sinomenina	т	_	460
		- î		71
C11H25O4N	Dubydrosinomenine	' 7 }	_ 1	71
CaHaONBr	Methyl-8-phenyl-1-keto-3-(bromo-4'-benny-	· 1	- 1	*1
	2',1')-6,7-indoldshydride-2,8		9.5	-
	R.P.1 6-Bromo-1-methyl-2-naphthylacetic acid	• 1	93	69
C14H14O ₄ S4	Thianthrene-chethylindandione	1	50	
C11H11O1CI		- 1	90	25
Millioici	Lactone of 2-(p-chloro-a-hydroxy-a-methyl-	1		
	benzyl)-1-naphthoic acid	11	70	265

Cto

CroII12O	1-Ketocholanthrene	IV	22	327
C ₂₀ H ₁₄ O	11-Acetylchrysene	11	-	193
$C^{10}\Pi^{14}O$	12-Acetylchrysens	II	53	198
CioHiiO	1-Keto-2a,3,4,5-tetrahydrocholanthrene	12	93	327
C10H11O	2-Keto-1,10-dimethyl-2,3,4,5,6,7,8,9,10,11- decahydrochrysene		1	279
CnHnO		I	39	
CasHuO.	Phenyl n-tridecyl ketone	1	39	471
C2011103	Lactone of 2-(a-hydroxy-8,a-dimeth) 1-2-		1	1
	naphthylmethyl)-benzoic acid	II	70	263
CtoH11Ot	Lactone of 2-(a-hydroxy-o,a-dimethylbensyl)-			J
	1-naphthose seid	11	76	220
C ₁₀ H ₁₅ O ₂	2,11-Diketo-5,14-dimethylbexshydrochrysene	111	63	444
C ₁₀ H ₁₀ O ₁	Lactone of 2-(a-hydroxy-6,a-dimethyl-7-			
_	tetrolylmethyl) benzose acid	II	36	272
CtoH11O1	Dimentyl dikelene	II	0	120
$C_{10}H_{14}G_{1}$	2,2,5,5-TetramethyRetrahydronaphtho-di-in-		1	(
	dan-4,6-dione	1	=	22
		I	-	26
C10H14O1	2,2-Diethyl-6,7-(2',2'-diethylcyclopenteno)-			
	indan-1,3-dione	I		13
$C_{10}H_{10}O_{1}$	2.2-Diethyl-5.6-(2',2'-diethylcyclopenteno)-	- 10		
	mdsn-1,3-dione	1		13
C _N II _N O ₁	Hinokione	I		430
CmHayO.	1.4-Myristylphenol	1	Q	10
CallarOs	4-II droxy-3,5-dimethylphenyl n-undecyl			
	ketone	I	45	106
CtoHaOa	Cycloercosan-1,11-dione	I	- 1	62
	R.P 2 Cyclogicosanone		V 1	

^{*} Q. Meld reported as quantitative, G. yield reported as good, P. Meld reported as poor. A dish indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp 201-209

I R.P., reduction product.

Formula	Compound	Method	Yield*	Refer- ence †
C ₂₀ H ₁₆ O ₃	5-Keto-8-methyl-5,6,7,8-tetrahydro-1,2-benz- 7-anthroic acid	ıv	61	445
$C_{20}H_{18}O_3$	Methyl α-methyl-β-(3-phenanthroyl)- propionate	I	P	151
$C_{20}H_{22}O_3$	Methyl α,α-spirocyclopentane-β-(4-methyl-1-naphthoyl)-propionate	I		241
C ₂₀ H ₃₀ O ₃ C ₂₀ H ₃₀ O ₃	3-Ketoetiocholanic acid 3-Ketoetioallocholanic acid	II	42	375 375
C ₂₀ H ₃₂ O ₃	2-Hydroxy-5-methoxy-4-n-pentylphenyl n-heptyl ketone	I		280
C ₂₀ H ₃₂ O ₃ C ₂₀ H ₁₄ O ₄	1-Myristyl-3,4-dihydroxybenzene 9,10,11,12-Tetraketo-2,6-dimethyl-	I		6
C20H18O4	9,10,11,12,15,16-hexahydronaphthacene 2,11-Diketo-5,14-dimethoxy-1,2,9,10,11,18-	I	_	157
	hexahydrochrysene	I I	47 45	136 186
C ₂₀ H ₁₈ O ₄	2,11-Diketo-6,15-dimethoxy-1,2,9,10,11,18- hexabydrochrysene	III	27	186
$C_{20}H_{22}O_4$	1,4-Di-p-anisoylbutane	III	62 43	387 183
$C_{20}H_{22}O_4$	1,6-Di-(2-hydroxy-4-methylphenyl)-hexane- 1,6-dione	I	_	168
C ₂₀ H ₂₅ O ₄ C ₂₀ H ₂₀ O ₅	3,11-(?)-Diketoetiocholanic acid 3,4'-Diethyl-2,3'-diformyl-6'-methoxy-5,6-	I	19	303
C20H34O6	methylenedioxy-1,1'-diphenyl ether 2,15-Dimethylhexadecane-5,12-dione-1,16-	III	_	316
	dicarhoxylic acid	I	_	168
C20H13OBr C20H23O5Br	2-(Bromoacetyl)-chrysene 1-(3',4'-Dimethoxyphenyl)-4-(2'-hromo-4',5'-	I		218
C20H17ON	dimethoxyphenyl)-hutanone-1 Dimethyl-3,8-phenyl-1-keto-2-(benzo-6,7-	I	93	159
	indoledihydride-2,8) R.P.‡ Methyl-(1-methyl-2-naphthyl)-accticacid	I		69
C20H18O4N	Berberinium Used Zn-Cd and Zn-Pb mixture R.P.‡ 16,17-Dihydrodesoxyberberin	I	92	294
C20N27O4N	Dihydromethylsinomenine	I	-	98
$C_{20}H_{17}O_6N$	Carbazole-3,6-bis-γ-ketobutyric acid	II	5 1 —	212 293

^{*} Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209.

[‡] R.P., reduction product.

C21

Formula	Compound	Method	Yield *	Refer-
C11H10O	5-Acetyl-2,2,4-triethyl-6,7-cyclohexenoindan	1	53	34
$C_{21}H_{42}O$	Dr-n-decyl ketone	I	31	234
C111120O1	Cryptomeria resm constituent	I	_	420
C11I110O3	Methylhinokione	I	- 1	430
C11H20O2	Methyl ether of sugnol	[i		431
C21H22O2	Allopregnanedione-3,20	11	- 1	267
		1 1	34	302
C1:11 12O1	Allopregnanedione-3,20	11	55	324
	R P.; Allopregnapone-20		11	
CnH ₁₂ O ₁	Pregnanedione-3.20	11	- 1	324
	R.P 1 Pregnanone-29		- 1	
CalHarOa	Uranedione-3.11	1 v 1	85	363
	R.P.t Uraneone-11	'		
CaHaO,	Uranedione-7.?	nt l	_	267
CarHa(Oa	Allopregnanol 20(a)-one-3	ii	10	334
CnH ₁₄ O ₂	3-Ethyl-4-hydroxy-5-methylphenyl n-undecyl			
	ketone	I	30	106
CatHasOa	Methyl & tetrahydroacephenauthroyl-pro-	- 1	**	
	pionate	1	35	476
CatHanO.	Allopregnagetrione-3.11.20	ī	71	302
	- marting - of 21,20	1Î		352
CatHaoCa	Allopregasnetrione-3,6,20	11	- 1	405
Cullao,	Uranetnone-3.11.20	Ÿ		363
	,	n l	- 1	367
	R.P.1 Uranedione-11.20		- 1	
CatHatOa	13-Keto-15-phenylpentadecanoic acid	1	94	189
Cat Has Oa	3,4-Dihydroxyphenyl s-tetradecyl ketone	- i		6
OuTtoO	Methyl 3.7-diketoetioallocholanate	11	30	374
IN ₁ O ₁ H ₁₄ O	Papaverin methiodide R.P.1 d.l-Laudenosin	1		294

...

Cn				
СыПпО	S-Acetyl-1,2-benzpyrens	11	24	328
C**H**O	1'-Keto-1',2',3',4'-tetrabydro-1,2-bearchrysene R.P.‡1'-Hydroxy-1',2',3',4'-tetrabydro-1,2- bearchrysens	11	-	300
CatH14O	?-Acetyi-12-ethylchrysene	1		213
Cullino	2,3-Diphenyltetralone-1	1	50	322
CnHnO	1'-Keto-3'-methyl-5.6-cyclopentenoretene	1		231
CuHuO	f-Butyl n-heptadecyl ketono	1	(-	234
C121111O1	1,2,3,4,5,5,7,8-Octamethylanthraquinone	1V	82	372

Q, yield reported as quantitative; G, yield reported as good, P, yield reported as poor. A dish
indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209

R P., reduction product.

Formula	Compound	Method	Yield*	Refer- ence †
C22H25O2	2,2-Diethyl-4,7-dimethyl-5,6-(2',2'-diethyl-			
	cyclopenteno)-indan-1,3-dione	I	88	12
C22H25O2	1,4-Myristylethoxybenzene	I	Q	10
C22H40O2	Cyclodocosan-1,12-dione	I	32	99
C=2H16O2	β-1-Chrysenoylpropionic acid	II	I —	300
C22H16O2	β-2-Chrysenoylpropionic acid	II	-	300
C+2H15O2	α,β-Diphenyl-β-benzoylpropionic acid	I	30	322
C22H22O2	β-S-Methyl-2-isopropyl-3-phenanthroyl-			
- 22 22 0	propionic acid	II	58	257
C21H22O2	Ketolactone from tigogenin	II	97	193
C22H24O2	3-Ketobisnorallocholanic acid	II	-	148
C22H25O2	1-Myristyl-3,4-dimethoxybenzene	I	l —	4
- 23 - 1 1		I	Q	10
	1	I	-	58
C22H25O2	1-(3',4'-Dimethoxyphenyl)-tetradecanone-3	I		6
C=-Hz=Oz	1-Myristyl-2,5-dimethoxybenzene	I	G	10
C22H25O4	1.4-Di-(p-ethoxybenzoyl)-butane	I	 -	183
C22H24O4	Keto acid from sarsasapogenin acetate	п	l —	355
C22H25O5	1-Keto-6,7-dimethoxy-2-(3',4'-dimethoxy-		1	
	benzyl)-3-methyl-1,2,3,4-tetrahydronaphtha- lene	I	50	275
CmHmOs	2.11-Diketo-5.6.14.15-tetramethoxy-		1]
- 22 - 23 - 0	1,2,9,10,11,18-hexahydrochrysenc	III	_	186
CarHarOr	4-Keto-6,7-dimethory-1-veratryl-3-methyl-			1
	1,2,3,4-tetrahydronaphthalene-2-carboxylic			
	acid	I	-	449
C22H24O2N2	N-Methyl-sccpsstrychnine	I	2	259

C23

				1
C22H11O	2-Benzylidene-3-phenyl-3-methyl-indanone-1	1	—	447
C22H44O	Cyclotricosanone	I		130
C22H44O	Di-n-undecyl ketone	lı	32	234
C22H21O	2-α-(α-Hydroxy-α,1'-naphthylethyl-1-	l	1	
	naphthoic acid lactone	ш	74	325
$C_{22}H_{22}O_{2}$	Methyl-6-acetyldehydroabietate	IV.	77	354
C22H2tO2	Allopregnanol-20(\$)-one-3-acetate	п		324
	R.P.; Allopregnanol-20(8)	1	ļ	ļ
C22H22O2	Pregnanol-20(a)-one-3-acetate	п		324
$C_{22}H_{23}O_{2}$	1-(2',3'-Dimethoxyphenyl)-pentadecanone-3	1		7
C21H21O2	1-(3',4'-Dimethoxyphenyl)-pentadecanone-3	I		6
$C_{23}H_{23}O_2$	3,4-Dimethoxyphenyl n-tetradecyl ketone	1		4
		I	!	58
C22H22O4	Tetrahydroanhydrosarmentogenone	II		223
			1	

^{*}Q. yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209.

² R.P., reduction product.

Formula	Compound	Method	Yield *	Refer-
CallagO ₄	Tetrahydroanhydrodigoxigenous	II		223
		II		205
CnH ₃₄ O ₄	Desoxypyrolithobihanic acid	11	-	59
CnH siO	Digitoxanondiacid	11	-	194
C23H22O1	Rotenone	1		104
C23II 12O1	Isorotenone	11	- 1	104
Cz.H.O,	Ethyl 4-keto-5,7-dimethoxy-1-verstryl-1,2,3,4- tetrahydronaphthalene-2-carboxylate	1	-	177
C11II160tCl	1,2,α-Triscetoxy-4-(p-chlorobenzyl)-naphtha- lene	1	-	321
	R.P.; 4-(p-chlorobenzyl)-1,2-dihydroxy- naphthalene		J.	

C2,

CtalleoO	Stearophenone	J III	77	1 450
		III	24	320
CtaHa0	Cyclohevyl n-heptadecyl Letone	1	45	234
CHILLO	2,2-Dimethyl-a-docosanone-\$	1	31	234
Calla0	2,2-Diethyl-4-methyl-7-isopropyl-5,6-(2',2'-			1
	diethylcyclopenteno)-indan-1,3-dione	1	73	25
ChillioO1	I 4 Palmity lethoxybensene	1	60	10
CHILLO	Cyclotetracosan-1,13-dione	1	39	99
CallaO	I-Cyclopentenyl-13-(2,4-dibydroxyphenyl)-)		1
- 41.041.	n-tridecanone-13	1 1	-	81
	(Chaulmoogryiresoremoi)	1	}	1
CallaOa	I-Cyclopentyl-13-(2,4-dshydroxyphenyl)-n-	1	1	1
-10-110-1	tridecanone-13	1 1	-	84
	(Dihydrochaulmoogrylresoremol)	1	Į.	1
CallaOs	Trihydroxycholene	1	- 1	407
Catlacoa	3.4-Dimethoxyphenyl n-pentadecyl ketono	1	1 0	4
011111001	CIA DIRECTOR OF THE CONTRACT O	1	Q	10
	ſ	1 1	-	58
CathadO	1.S-Di-p-anisoyloctane	III	59	387
Callao	Dehydrohyodesoxycholie acid	11	-	42
Callao.	3,12-Diketocholamo acid	l v	-	463
Oftrigor	R P.1 12-Ketocholame acid	1		
Callao	3.Hydroxy-7-ketocholanic acid	{ z	-	237
Cull to O4	Ursodesoxycholic acid	и	-	461
CHILLO	Debydyscholio scid	II	_	23
Official	R.P.\$ 7,12-Diketocholanic seid	11	-	462
		11	-	18
CHII NO	a-Triketocholsnie seid	11	11111	434
CHILLO,	Dehydrocholic acid	11		32
alterito 1	1	11	-	423
		11		23
Culling	Diothil S.S. di-p-ensyl-3.S. dibydroxyedipate	[t (137

^{*} Q, yield reported as quantitative: G, yield reported as good, P, yield reported as poor A dash indicates that the yield is not reported

[†] Reference numbers refer to the bebliography on pp. 201-209,

R.P., reduction product.

C25-C25

	C ₂₅ —C ₂₆			
Formula	Compound	Method	Yïeld*	Refer- ence †
C22H16O	12-Benzoylchrysene	II	79	193
C21H21O2	1-Cyclopentenyl-13-(2-hydroxy-4-methoxy-		l	
	phenyl)-n-tridecanone-13	I	-	84 268
C2:H2:O;	Pregnandiol-3,4-one-20 dizcetate R.P.: Allopregnane	II	_	203
C25H42O	2-n-Pentadecyl-5,6,7,8-tetrahydronaphthyl ketone	11	63	358
C2:H2:O2	1,2,3,4,5,6,7,8-Tetracyclopentenoanthra-		73	372
	quinone	IV	51	99
C_2 ; H_4 ; O_2	Cyclohexacosan-1,14-dione	I	51	"
C25H4:Oz	1-Cyclopentenyl-13-(2,4-dimethoxyphenyl)-	_		S4
	n-tridecanone-13	I	80	128
C25H44O2	Ketocarboxylic acid obtained from cholesterol	II II	75	65
		•	<u></u>	
	C ₂₇			
C ₂₇ H ₄₅ O	Cholestanone-6	II	-	469
CzzH45O	Cholestanone-7	V	-	326
C::H::O	Zymostanone	II	-	472
C=HHO	14-Heptacosane (myristone)	I	=	127
C=7H44O2	Desorysarsasapogenone	п	-	354
Cz:H40:	Cholestanedione-3.6	V		326
		II	 —	233
C27H4402	Epicoprostanol-3-one-24	II	0	210
C=H4:O:	Sarsasapogenone	IV	63	359
0,,,=0,-0		V	45	354
		п	S1	323
		IV	43	308
C27H42O2	Ізозагвазароденопе	v	_	323
02,114204		п	_	323
$C_{zz}H_{4z}O_z$	Pseudosarsasapogenone	v	 	359
C=:H42O2	Tigogenone	7		367
05,114,50	2.696.2000	11	P	353
		7	1 -	357
C27H44O1	Tigogenin	11	l —	357
C _T H ₄ ;O ₄	Anhydrosarsasapogenoic acid	II	20	303
Cz:H4:O4	Chlorogenone	v	_	326
02,124,04	31107082113110	11	_	367
C=:H46Os	Ketodicarboxylic acid from cholestanone	II	1 -	28
C ₂₇ H ₄₂ O ₇	6-Ketolithobilianic seid trimethyl ester	II	_	59
Catheon	Solatubenone	ī	I -	411
C=H=O,N	9-o.m.p-Tolyldesoryberberin	II	G	170
CHH504N	9-Phenyldesoxypalmatin	I		294
	R.P.: 9-Phenyl-2,3,11,12-tetramethoxyberbin	_	1	
Cz:Hz:OzN	9-o-Anisyldesoxyberberin	II	G	170

^{*} Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dash indicates that the yield is not reported.

[†] Reference numbers refer to the hilliography on pp. 201-209.

¹ R P., reduction product

Formula	Compound	Method	Yield *	Refer
CnH ₄₀ O	Ergustatrienone	1	_	123
CnH ₁₂ O	a-Ergostadienone	tif	_	123
CHII40	a-Ergostenone	1 1	_	123
Cull ₁₁ 0	2-n-Heptadecyt-5,6,7,8-tetrahydronaphthyl	1 1		
	ketone	111	as	450
Call ₄ O ₁	Campanepermonyl metyl ether	I		85
CnH 102	Cyclo-octarosan-1,15-dione	1 1	51	99
Cnllu0i	13-Keto-22-phenylbehenic acid	fil	30	189
CMIMO*	Ergostanedional	I II	/	162
Cp.II.coOs	Triketohufosterochtlenie acid	1 11 /	- 1	459
CMII4O	Triketoisosterocholenie aeid	1 1		453
C ⁶ 3I ⁴⁶ O ²	Triketobulosterocholanie acid	1 11 1	_	459
CallnOaN	9-Verairs idesoxyberbenn	11	6	170

Cm				
СыПиО	Norechinocystenone	11		393
CpII40	Oleanope	[T		456
	l .	11		473
Cuff 40	2-Methyl-3-n-pentadecyl-5,6,7,8-tetrahydro-	ł		1
	naphthyl ketone	п	60	383
C _P H _P O	Bombieestanone	1		281
		11	72	388
CnII nO	Inagostanone	11	_	282
Callao	Cyclononacosanono	1	-	99
CHILLO	15-Nonacosanone (Isurone)	I		127
CnH,O	9-Nonacosanone	1		127
CnIIaO	10-Nonacosanone	1		127
CHILIO	12-Nonacosanone	1		127
Cull ₁₄ O ₁	Norechinocystendione	11	-	392
Cull ₄ O ₁	Sapogenol diketone	11	-	247
C24 1142 O4	Diketolactone of quillaio acid	11	-	379
CmII stO4	5-Hydroxy-3-stearoyl-4,6,7-trumethylisocou- maisuone	11	Q	277

Q, yield reported as quantitative, Q, yield reported as good, P, yield reported as poor. A dash indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp 201-209 ‡ R.P., seduction product.

C₃₉-C₃₁

Formula	Compound	Method	Yield *	Refer- ence †
C22H44O	n-Heptadecyl hiphenyl ketone	ш	73	450
C25H55O	Lupanone	п	<i>-</i>	443
C2:H550	Cyclotriacontanone	I	34	S2
C25H2*O*	1,2,3,4,5,6,7,8-Tetracyclohexenoanthraquinone	IV	82	372
CacHssO.	Cyclotriacontan-1,16-dione	1	51	82
Callings	0,000	1	32	99
$C_{20}H_{45}O_{2}$	Oleanonic acid	п	_	245
C27H3/O2	Methyl hedragon	11	 	347
C2:H5:O2	13-Keto-n-triacontanoic acid	I		160
C2:H44O4	Methyl ester of diketoquillaic acid	11	60	379
CrHs:0s	14-Keto-octacosane-1.28-dicarboxylic acid	1	l —	82
C20H25O4N	9-a-Naphthyldesoxyberberin	Π	G	170
C21H32O	ar2-Methyl-3-phytyltetralin	II	95	383
Ca1He2O	16-Hentriacontanone (pelmitone)	1	_	127
C21H41O2	Methyl oleanonate	п	l —	245
C21H45O4	Oxidation product of methyl echinocystate	11	85	352

C32---C57

C23H66O2	Cyclodotriacontan-1,17-dione	1	-	171
C32H44O4	Ergosteron-3-maleic anhydride addition	п	35	204
CzzH44Os	Ketoacetyloleanolic acid	II	<u> </u>	245
C22H24O4	Diacetate of 4-hydroxystigmastanol R.P.‡ Stigmastane	11	_	269
C24H2:O2	3,9-Dibenzoylperylene	I	-	105
C24He4O2	Cyclotetratriacontan-1,18-dione	I	_	171
CuH(O2	13-Ketotetratriacontanoic acid	I	80	229
CzsHz:0	Pentatriacontanone-18 (Stearone)	I	l —	127
	,	I	Q	1
C25H45O4	Ketone acetate from desoxysarsasapogenin	11	6	308
$C_{23}H_{22}O$	Triphenylmethyl 4-(diphenylmethyl)phenyl		ł	
	ketone	I	l —	70
C41H24O2	Tribenzoylperylene	II	1 —	199
	R.P.‡ Benzyldibenzoylperylene	1		1
$C_{42}H_{22}O_2$	13-Ketohexatetracontanoic acid	I	86	229
Ce7H124O	n-Heptahexacontanone-34	1	-	229

^{*} Q, yield reported as quantitative; G, yield reported as good; P, yield reported as poor. A dust indicates that the yield is not reported.

[†] Reference numbers refer to the bibliography on pp. 201-209.

[#] R.P., reduction product.

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CHAPTER 8

THE PERKIN REACTION AND RELATED REACTIONS

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INTRODUCTION

In 1868 W. H. Perkin ¹ described a synthesis of coumarin by heating the softium salt of salicylaldehyde with acetic anhydride. Further study of this reaction led to the discovery of a new method for preparing cinnamic acid and its analogs by means of a synthesis of very general application, which became known as the Perkin reaction.² This reaction is brought about by heating an aldehyde of aromatic type with the anhydride of an aliphatic acid of the general formula RCH₂CO₂H, in the presence of the sodium salt of the acid.

$$\begin{array}{lll} C_{1}\Pi_{1}C\Pi=0+(C\Pi_{1}CO)_{2}O+C\Pi_{1}CO_{3}N_{\Delta} \rightarrow C_{1}\Pi_{1}C\Pi=CHCO_{3}\Pi \\ C_{2}\Pi_{1}C\Pi=0+(RC\Pi_{1}CO)_{2}O+RC\Pi_{2}CO_{3}N_{\Delta} \rightarrow C_{1}\Pi_{1}C\Pi=CCO_{3}\Pi \\ &\vdots \\ \end{array}$$

Since the resulting β -arylacrylic acids can be subjected to a variety of chemical transformations, the Perkin reaction gives access indirectly to a number of other types of compounds such as arylethylenes and acetylenes, arylacctaldehydes, arylethylamines, arylpropionic and propiolic acids, and their derivatives. Several modifications and extensions of the Prekin reaction, such as the paraconic acid synthesis of Fittig and the azlactono synthesis of Erlenmeyer, have served to broaden the scope and usefulness of the original process.

In the course of an extensive study of unsaturated acids Fittig 3 and his collaborators made several important contributions to the mechanism of the Perkin reaction. He showed that the adehyde condenses with the afpha methylene group of the acid component (salt or anhydride) and concluded that the reaction is an addition process, like an addol condensation, involving an intermediate β -hydroxy compound that loses water to form the α -funsaturated acid.

$$\begin{array}{c} C_4H_1CH=O+(CH_2CH_2CO)_2O+CH_2CH_2CO_2Na \rightarrow \\ & & & & & & & & \\ C_4H_4CHOHCHCO_2H & & & & & \\ CH_3 & & & & & & \\ CH_3 & & & & & & \\ \end{array}$$

Perkin ² had assumed, without experimental proof, that the carbon atom farthest removed from the carboxyl group was probably the one which

Perkin, J. Chem. Soc., 21, 53, 181 (1968)

Perkin, J. Chem. Soc., 31, 388 (1877).
Fittig, Ann., 195, 169 (1879), 216, 67 (1883); 227, 48 (1885); Ber., 14, 1824 (1881)
Ed., 1436 (1883), 27, 2685 (1897).

condenses with the aldehyde, but Fittig and others, 4-1 quickly dis-

proved Perkin's tentative hypothesis.*

The view that the Perkin reaction involves an intermediate addition product of the aldol type is generally accepted at the present time. It is supported by the actual isolation of derivatives of the intermediate addition products in certain cases where the normal elimination of water does not occur. For example, benzaldehyde, sodium isobutyrate, and isobutyric anhydride (or acetic anhydride) on heating at 100° give rise to the isobutyryl derivative of 3-phenyl-3-hydroxypivalic acid (a,a-dimethyl-3-hydroxy-3-phenylpropionic acid)⁵ and the mixed anhydride of this acid with isobutyric acid.

$$C_{t}H_{z}CH=0\div(CH_{z})_{z}CHCOOCOCH(CH_{z})_{z}\div(CH_{z})_{z}CHCO_{z}Nz\rightarrow\\ C_{t}H_{z}CH=C(CH_{z})_{z}CO_{z}H\ \ and\ \ C_{t}H_{z}CH=C(CH_{z})_{z}COOCOC_{z}H;\\ \dot{O}COC_{z}H_{z} \qquad \dot{O}COC_{z}H_{z}$$

The total yield, calculated as \$-phenyl-\$-hydroxypivalic acid, is about 33% of the theoretical. At 150° the same reactants give the unsaturated hydrocarbon, 2-methyl-1-phenylpropene, which is formed presumably from the above intermediates by loss of carbon dioxide and isobutyric acid (or anhydride).

$$C_{\varepsilon}H_{\varepsilon}CH - C(CH_{\varepsilon})_{\varepsilon}CO_{\varepsilon}H \rightarrow C_{\varepsilon}H_{\varepsilon}CH - C(CH_{\varepsilon})_{\varepsilon} \div CO_{\varepsilon} \div C_{\varepsilon}H_{\varepsilon}CO_{\varepsilon}H$$

 $OCOC_{\varepsilon}H_{\varepsilon}$

Likewise, furfural on heating with isobutyric anhydride and softum isobutyrate gives only 2-methyl-1-furylpropene, even at temperatures as low as 100°.

In typical examples of the Perkin reaction, involving derivatives of acetic acid or monosubstituted acetic acids, decarboxylation has been observed in a few instances, notably with isovaleric acid. This side

^{*} For an interesting account of early work on the Perkin reaction see Lackmann, "The Spirit of Organic Chemistry." The Macmillan Co., London (1899), pp. 12-201 also, Colem-Organic Chemistry for Advanced Students." Eith edition, Longmans, Green and Co., New York (1928), Part I, pp. 288-293. An excellent review of recent work is given by Watson Ann. Bepte. Ciem. Son (London, 25, 210 (1939).

Bueyer and Jackson, Ber., 13, 115 (1880).
 Course and Bischoff, April, 204, 183 (1880).

Fintig and Jayres, Ann., 215, 115 (1883.; Fintig and On., Ann., 227, 119 (1885..

^{*} Harser and Breslow, J. Am. Chem. Soc., 51, 723 (1909).

Perkin, J. Cum. Soc., 25, 128 (1979).
 Busyer and Tomies. Ben. 10, 1864 (1977).

[&]quot; Scharzehmitt, Georges-opel, auf Hersenberg, Br., 51, 1959 (1918).

reaction is generally negligible at the temperatures usually employed (140-175°) but may become important at higher temperatures. Thus. anisaldehyde on heating at 170° with propionie anhydride and sodium propionate yields mainly p-anisyl-a-methylacrylic acid,11 but at 200° anethole (p-propenylanisole) is obtained u

Further evidence for the formation of an intermediate of the aldol type is afforded by the reaction of benzaldehyde with succinic anhydride (or acetic anhydride) and sodium succinate. Fittig and Jayne " showed that if the reaction is carried out at 100° the product is \gamma-phenylparaconic acid, formed by lactonization of the intermediate hydroxy acid.

Phenylmocrotomic scid

On heating to 150°, \gamma-phenylparaconic acid loses earbon dioxide and gives the \$,7-unsaturated acid, phenylisocrotome acid, which Perkin had obtained directly by carrying out the original condensation at 150°. The relative significance of the acid anhydride and the sodium salt in

the intimate mechanism of the Perkin condensation has been the subject of numerous investigations extending over a period of more than fifty years. Perkin believed that the cinnamic acids are formed by condensation between the aldehyde and the acid anhydride, with the sodium salt functioning as a catalyst. He found that cinnamic acid is formed alone when benzaldehyde and acetic anhydride are heated at 180° with sodium acetate, butyrate or valerate, whereas benzaldehyde on heating with propionic anhydride and sodium acetate gives only α-methylcinnamic acid. Fittig then studied the reaction with several anhydride-salt combinations, particularly at lower temperatures. He found that benzaldehyde, acetic anhydride, and sodium acetate (in equimolecular amounts) do not react at 100° even on long-continued heating; when sodium n-butyrate was used in place of the acetate, reaction occurred slowly and only α -ethyleinnamic neid was formed, but at 150° a mixture containing one part of a-ethylcinnamic to two parts of cinnamic acid was obtained, and at 180° the product contained only one part of

¹¹ Perkin, J. Chem. Soc., 31, 415 (1877); 32, 669 (1878).

¹¹ Moureu and Chauvet, Buil. soc. chim., [3] 17, 412 (1837); Moureu, Ann. chim., [7] 15, 135 (1898).

¹¹ Fittig and Jayne, Ann., 216, 100 (1883).

tion mixture and the product is made up of about 30% of α -ethylcinnamic and 70% cinnamic acid.

Fittig's view that the salt condenses with the aldehyde appeared to be strongly supported by Stuart's observation "I that benzaldehyde, sodium malonate, and acetic anhydride react at room temperature with evolution of carbon dioxide and formation of cinnamic acid. Fittig regarded this as a convincing proof of his view since he believed that randonic acid was incapable of forming an anhydride and the reaction must have occurred between the aldehyde and sodium malonate. Michael pointed out that this argument also is not valid since a mixed anhydride of malonic and acetic acid could be formed and, in any event, malonic acid is much more reactive in condensation reactions than the anhydrides or salts of monobacie acids. This view is confirmed by recent work "which has shown that sodium malonate does not react with benzaldehyde to any appreciable extent unless glacial acetic acid is present.

In spite of Michael's objections, Fittig's interpretation was widely accepted for many years and still persists in several of the current textbooks of organic chemistry. However, the results of a number of workers now provide substantial evidence in favor of Perkin's and Michael's view that it is the anhydride and not the salt that undercoes condensation with the aldehyde. Kalnin 18 has shown that benzaldehyde condenses readily with acetic anhydride in the presence of inorganic and organic bases (potassium carbonate, triethylamine, etc.) but does not condense with sodium acetate in the presence of these catalysts (or in the presence of inorganic dehydrating agents 19). These and other results 20-21 indicate that the Perkin reaction is essentially an aldol condensation of the aldehyde and anhydride, in which the salt of the acid functions merely as a base and promotes enolization of the anhydride. In this connection it is of interest to note that ketene, which may be regarded as an intramolecular anhydride of acetic acid, reacts readily at 25° with benzaldehyde in the presence of potassium acetate to give a mixed anhydride of cumamic and acetic acids, along with styrene.22

$$\begin{array}{c} \text{C}_{6}\text{H}_{1}\text{CH}0 + 2\text{CH}_{2} = \text{C} = 0 \xrightarrow{\text{CH}_{3}\text{CO}_{3}\text{K}} & \text{C}_{4}\text{H}_{1}\text{CH} = \text{CHC00C0CH}_{1} \\ \\ \text{C}_{4}\text{H}_{1}\text{CH}0 + \text{CH}_{2} = \text{C} = 0 \xrightarrow{\text{C}_{3}\text{H}_{3}\text{CH}} = \text{CH}_{2} + \text{CO}_{2} \\ \end{array}$$

This reaction does not take place with tributylamine in place of potassium acetate, and with small amounts of the latter (0.1 mole per mole of

¹⁴ Kalnin, Hely, Chim Acta, 11, 977 (1928).

Bakurun and Peccerillo, Gazz. chim. stal., 65, 1145 (1935).
 Kubn and Ishikawa, Ber., 64, 2347 (1931).

¹¹ Maller, Ann., 491, 251 (1931).

[&]quot; Hurd and Thomas, J. Am. Chem. Soc., 65, 275 (1933).

benzaldehyde) produces about 70% of styrene and only 30% of cinnamic acid.²³

Perkin ²⁴ suggested that the aldehyde and anhydride combine to form benzal diacetate, which then undergoes rearrangement under the influence of sodium acetate.

$$\begin{array}{c} C_6H_5CH(OCOCH_3)_2 \xrightarrow{|CH_3CO_2N_0|} C_6H_5CH-CH_2CO_2H \xrightarrow{} \\ |\\ OCOCH_3 \\ |\\ C_6H_5CH-CHCO_2H \end{array}$$

The intermediate formation of benzal diacetate appeared plausible in view of Caro's synthesis ²⁵ of cinnamic acid by heating benzal chloride with excess sodium acetate. This idea was elaborated by Nef, ²⁶ who postulated the formation of the nascent phenylacetoxymethylene radical, C₆H₅—CH—OCOCH₃, in the process. Experiments showed, however, that benzal diacetate and sodium acetate give only small amounts of einnamic acid at 160–180° under the usual conditions of the Perkin reaction, and higher temperatures (200–220°) are required to obtain a good conversion. Other work ²⁷ indicates also that the aldehyde diacetates are not intermediates in the Perkin reaction, but that they react by decomposing into the aldehyde and acid anhydride.

The modern view of the mechanism of the Perkin reaction is essentially that the aldehyde reacts with the sodium salt of the enol form (enolate anion) of the acid anhydride, formed by interaction of the anhydride with the sodium salt or other base; the addition product then decomposes into cinnamic acid.

The intimate details of the process may be envisaged in several ways,^{7, 22} all leading to the same result. The notion of enolization of the anhydride is supported by Müller's observation ²¹ that the sodium derivative of homophthalic anhydride reacts smoothly with benzaldehyde at room

²³ Vittum, Thesis, Cornell University, 1933.

²⁴ Perkin, J. Chem. Soc., 31, 424 (1877); 49, 317 (1886).

²⁵ Ger. pats., 17,467, 18,232 (1880) (Frdl., 1, 26, 28).

²⁶ Nef, Ann., 298, 302 (1897); see also references 174 and 175, p. 264.

²⁷ Böck, Lock, and Schmidt, Monatsh., 64, 401 (1934).

temperature. This reaction is analogous to the paraconic acid syntheses involving succinic anhydride, and leads eventually to a lactone-acid.

Likewise, Hauser and Breslow † have shown that benzaldehyde reacts instantly at room temperature with the sodium enolates of ethyl acetate and isobutyrate to form β -phenyl- β -hydroxy esters.

SCOPE OF THE REACTION

The Perkin reaction may be regarded essentially as the condensation of a carbonyl component A and an acid anhydride-salt combination B. In the resulting acrylic acids, substituents in the carbonyl component appear in the β -position and those in the acid component appear in the exposition.

The following discussion gives a survey of the types of carbonyl components and acid anhydride-salt combinations that can be used, and of the yields that can be obtained under favorable conditions.

Carbonyl Components

In general the usual Perkin reaction is limited for practical purposes to aldebydes of the aromatic series and closely related types. Table I gives a brief survey of the yields of β-arylscrylic acids obtained from various substituted benzaldebydes, with acetic anhydride and sodium acetate,

under similar conditions of reaction. 27, 23, 29 The yields given are typical but do not always represent the maximum that can be secured with a given aldehyde, as the optimum conditions of reaction (temperature, duration of heating, catalytic effects, etc.) vary somewhat for different substituents.

TABLE I YIELDS OF CINNAMIC ACIDS FROM SUBSTITUTED BENZALDEHYDES a

Substituent	Yield (per eent)	Substituent	Yield (per cent)
None 27	45-50 t	2-Methoxy 12	55
2-Methyl =7	15	2,5-Dimethoxy 21	56
3-Methyl 27	23	4-Methoxy 22	30
4-Methyl 27	33	4-Ethoxy 12	36
2,6-Dimethyl 27	0	4-Hydroxy 27	62
2-Iodo 23	85	4-Dimethylamino 27	0
2-Chloro 27	71	2-Nitro 27	75
3-Chloro ==	63	3-Nitro 27	75
4-Chloro 27	52	4-Nitro 27	82
2,6-Dichloro 27	82	2,4-Dinitro 27	70 °

⁴ The conditions were very similar but not identical in all experiments. In general, 1 mole of the aldehyde was heated for eight hours at 180° with about 2 moles of acetic anhydride and 0.7 mole of zodium acetate.

sodium acetate.

b It has been reported that the yield of cinnamic acid can be increased to 89-85% by adding a little pyridine as entalyst; this result could not be checked in the Cornell laboratory. The yield is increased to 70-75% (without addition of pyridine) by heating for twenty-four hours. The yield is obtained with eight hours heating at 150°; with four hours' heating at 180° the yield is about 20%, and longer heating gives lower yields.

These results indicate that the activity of substituted benzaldehydes in the Perkin reaction is similar to the trends observed in other reactions involving the carbonyl group. A halogen or nitro group in any position increases the rate of reaction and the yield; a methyl group in any position decreases the rate and the yield, and this effect falls off in the order: ortho > meta > para. A methoxyl group in the ortho position has a small favorable influence, but in the para position it has a definitely unfavorable effect on the rate and the yield.

The behavior of ortho-substituted benzaldehydes indicates that the reaction is not adversely affected unless the type of substituent is unfav-Thus, 2,6-dichlorobenzaldehyde and 2,6-dinitrobenzaldehyde orable.

²³ Lock and Bayer, Ber., 72, 1064 (1939).

²² Meyer and Beer, Monatch., 34, 649 (1913).

²⁰ Posner, J. prakt. Chem., [2] 82, 425 (1910).

²¹ Kauffmann and Burr, Ber., 40, 2355 (1907).

²² Stoermer, Ber., 61, 2326 (1928).

²² Bacharzch and Brogan, J. Am. Chem. Soc., 50, 3333 (1928).

give excellent yields, but 2,6-dimethylbenzaldehyde and 2,4,6-trimethylbenzaldehyde do not react appreciably.²⁷

Substituted bentaldehydes with hydroxyl groups in the meta or para positions give satisfactory results. In the course of reaction the hydroxyl group is acetylated and the product is the corresponding acetoxycinnamic acid. The latter need not be isolated and can be saponified readily to give the free hydroxy acid. Salicylaldehyde gives commarin, the lactone of the cis form of e-hydroxycinnamic acid (commarinic acid), together with the acetyl derivative of the trans form (commarie acid).

The action of alkalies on coumarin gives salts of coumarinic acid, but the acid is unknown in the free state as it undergoes ring closure spontaneously to regenerate coumarin. Strong alkalies or alcoholic sodium ethoxido convert coumarin into salts of coumarin acid, from which the free acid can be obtained by acidification. Methylation of sodium coumarnte gives trans—methoxyetinnamic acid, which is identical with the acid obtained from o-methoxyetinnamic acid, which is identical with the acid obtained from o-methoxyetinnamic acid, which is identical with

The aminocinamic acids are not prepared directly by the Perkin reaction but are obtained by reduction of the corresponding nitrodinnamic acids with ferrous sulfate and ammonia. The ordinary (stable) form of a-nitrocinamic acid, obtained from a-nitrobenzaldehyde in the Perkin reaction, gives trans-a-uninocinamic acid, which on long heating with hydrochloric acid is converted to carbostyril (the nitrogen analog of countrie). **

The aminocinnamic acids can be diazotized and subjected to the usual diazonium replacement reactions; this method has served for the preparation of the chloro-, bromo-, and iodocinnamic acids, ³² and o- and p-fluorocinnamic acids, ³³

³⁴ Tiemann and Herzfeld, Ber., 10, 285 (1877).

³⁶ Gabriel, Ber., 15, 2294 (1882); Gabriel and Hersberg, Ber., 16, 2038 (1883).

³⁵ Baeyer and Jackson, Ber., 13, 115 (1880); Themann, Ber., 13, 2069 (1880); Posner Ann., 389, 45 (1912); Stoermer and Heymann, Ber., 45, 3099 (1912).

[&]quot; Griess, Ber., 18, 961 (1885), Kindler, Ann., 464, 278 (1928).

The Perkin reaction has been carried out with aldelydes of the biphenyl ³⁸ and naphthalene series. 1-Naphthaldelyde ³⁹ and 4-bromo-1-naphthaldelyde ⁴⁰ react quite satisfactorily, but 2-naphthaldelyde ³⁹ gives only a small yield of β -2-naphthylacrylic acid. 2-Hydroxy-1-naphthaldelyde gives a 30% yield of β -naphthocoumarin.⁴¹

Furfural ⁴² (and substituted 2-furanaldehydes) and 2-thiophenealdehyde ⁴³ take part readily in the Perkin reaction, but there appears to be no report of the use of aldehydes of the pyridine and quinoline series. The 2- and 4-pyridineacrylic acids, and the corresponding quinoline derivatives, are prepared conveniently by condensation of the 2- or 4-methyl derivative with chloral, followed by hydrolysis.⁴⁴

$$\overbrace{\mathbb{Q}_{N}}^{\text{CH}_{2}+\text{CCl}_{2}\text{CHo}} \xrightarrow{\text{ZnCl}_{2}} \overbrace{\mathbb{Q}_{N}}^{\text{ZnCl}_{2}} \xrightarrow{\text{CH}_{2}\text{CHoHCCl}_{3}} \xrightarrow{\text{KoH}} \overbrace{\mathbb{Q}_{N}}^{\text{KoH}} \xrightarrow{\text{CH}=\text{CHCO}_{2}\text{H}}$$

The condensation of indole-3-aldchyde with hippuric acid in the presence of acetic anhydride and sodium acetate (Erlenmeyer's azlactone synthesis) has been reported.⁴⁵

Cinnamaldehyde, which is a vinylog of benzaldehyde, gives excellent yields of β -styrylaerylic acids under the usual conditions of the Perkin reaction.²

reaction.²

$$C_6H_5CH = CHCHO + (CH_3CO)_2O \xrightarrow{CH_3CO_2N_B} C_6H_5CH = CHCH = CHCO_2H$$

On heating einnamaldehyde with phenylacetic acid in the presence of acetic anhydride and litharge, decarboxylation occurs and 1,4-diphenyl-butadiene is obtained in 30% yield.⁴⁶

C₆H₅CH=CHCH=CHC₆H₅

²⁸ Hey, J. Chem. Soc., 2478 (1931); see also Vorländer, Ber., 68, 453 (1935), and reference 28, p. 1069.

²⁹ Rousset, Bull. soc. chim., [3] 17, 813 (1897).

⁴⁰ Mayer and Sieglitz, Ber., 55, 1839 (1922).

⁴¹ Kaufmann, Ber., 16, 685 (1883).

⁴² Baeyer, Ber., 10, 357 (1877); Gibson and Kahnweiler, Am. Chem. J., 12, 314 (1890); Johnson, Org. Syntheses, 20, 55 (1940).

⁴³ Biedermann, Ber., 19, 1855 (1886); Cohn, Z. physiol. Chem., 17, 283 (1890).

⁴⁴ Einhorn, Ber., 18, 3465 (1885); Ann., 287, 27 (1895); Koenigs and Miller, Ber., 37, 1338 (1904); Rabe and Kindler, Ber., 55, 532 (1922); Alberts and Baehman, J. Am. Chem. Soc., 57, 1284 (1937).

⁴⁵ Ellinger and Flamand, Ber., 40, 3031 (1907); Z. physiol. Chem., 55, 15 (1908).

⁴⁶ Kuhn and Winterstein, Helv. Chim. Acta., 11, 103 (1928); Corson, Org. Syntheses, 16 28 (1936).

Under the same conditions two moles of cinnamaldehyde react with one of succinic acid to give 1,8-diphenyloctatetrene.44

The bifunctional aromatic aldehydes, phthalaldchyde, " isophthalaldehyde. 43 and terephthalaldehyde, 45- 40 can be converted to the corresponding benzenediaerylic acids in 20, 80, and 50% yields, respectively. Under mild conditions terephthaldeligde gives the monoacrylic acid, 4-formylcinnamic acid; " on prolonged heating a mixture of the monoand di-acrylic acids is obtained (25% and 50% yields, respectively). 40

2.2'-Biphenyldialdehyde gives an 8-9% yield of 2.2'-biphenyldiacrylic neid 1

4-Cyanobenzaldchyde and 4-carboethorybenzaldchyde have been converted to the corresponding einnamic acids, apparently in satisfactory yields. 2-Cyanocinnamie acid has been prepared through Caro's modification of the Perkin reaction, by heating 2-evanobenzal chloride with acetic anhydride and sodium acetate.

Aliphatic aldehydes such as valeraldehyde and heptaldehyde give mainly condensation products when heated with acetic aphydride and sodium acetate, and only small amounts of the 6-alkylaerylic acids are formed.14 Acetaldchyde with propionic anhydride and sodium propionate (thirty hours at 120-130°) gives a small yield of tiglic acid, and isobutyraldehyde with the same reagents (thirty hours at 190-200°) gives a 15-20% yield of isomeric 4-methylpentenoic acids. The reaction with sodium phenylacetate and acetic anhydride, sometimes called Orlialoro's modification of the Perkin reaction,44 is somewhat more satisfactory; with these reagents paraldehyde gives a phenylcrotonic acid (methylatropic acid).17

⁴⁷ Thiele and Falk, Ann., 347, 117 (1906).

⁴ Ruggli and Staub, Hele. Chim. Acts, 17, 1523 (1934).

⁴⁹ Low. Ann., 231, 375 (1885). M Ephram, Ber., 34, 2784 (1901).

⁴¹ Westzenbock, Monaish., 34, 208 (1913).

¹⁴ Mores, Ber., 33, 2625 (1900); see also Shoppee, J. Chem. Soc., 985 (1930).

⁴⁴ Drory, Ber., 24, 2574 (1591). Fittig and Schnergans, Ann., 227, 79 (1885), Fittig and Höffken, Ann. 304, 334 (1899).

⁴⁴ Kietreiber, Monatsh., 19, 735 (1898). M Oghaloro, Gazz, chim. stal., 8, 429 (1878); 9, 428, 432 (1875); 10, 481 (1880); and later papers.

⁴¹ Rupe, Ann., 369, 332 (190-).

Although the Perkin reaction in its simplest form is quite unsatisfactory with aliphatic aldehydes, modifications involving the replacement of the monobasic acid components by succinic acid (Fittig's synthesis of paraconic acids and β,γ -unsaturated acids)^{13,54,58} and by malonic acid (Doebner,⁵⁹ Knoevenagel ⁶⁰) are useful preparative methods in the aliphatic and aromatic series.

Simple aliphatic and aromatic ketones cannot be used as carbonyl components in the Perkin reaction, or in the paraconic acid synthesis. Acetone condenses with malonic acid in the presence of acetic anhydride, or ammonia, to give β , β -dimethylacrylic acid. The best results are obtained by Doebner's method using malonic acid and pyridine, which gives a 60% yield; and under these conditions diethyl ketone gives β , β -diethylacrylic acid in 30% yield, but cyclohexanone gives less than 5% of the corresponding acrylic acid.

 α -Ketonic acids react with acetic anhydride and sodium acetate, with loss of carbon dioxide, to give β -substituted acrylic acids. ⁵⁴ Pyruvic acid gives crotonic acid, and arylglyoxylic acids give the corresponding cinnamic acids.

$$RCOCO_2H + (CH_3CO)_2O \xrightarrow{CH_2CO_2Na} RCH = CHCO_2H + CO_2 + CH_2CO_2H$$

Pyruvic acid reacts in a similar way with sodium succinate in the presence of acetic anhydride, to form dimethylmaleic anhydride. These reactions have little preparative value as the same products can usually be obtained from more readily accessible reactants.

Michael and Gabriel made the remarkable discovery that phthalic anhydride may be used as the carbonyl component in a Perkin reaction. On heating phthalic anhydride with acetic anhydride and potassium acetate, for ten minutes at 150–160°, phthalylacetic acid is formed in 50% yield. 65

$$\begin{array}{c}
\text{HCCO}_2\text{H} \\
\text{CO} \\
\text{CO}
\end{array}$$

$$\begin{array}{c}
\text{CH}_3\text{CO}_2\text{K} \\
\text{CO}
\end{array}$$

- ²⁵ Fittig and Frankel, Ann., 255, 18 (1889); Fittig and Politic, Ann., 255, 293 (1889).
- 13 Doebner, Ber., 33, 2140 (1900); Ber., 35, 1137 (1902).
- ⁶⁹ Knoevenagel, Ber., 31, 2598 (1898); Ger. pats., 97,734, 156,560, 161,171 (Frdl., 7, 736; 8, 1268).
 - 61 Massot, Ber., 27, 1225, 1574 (1894).
 - ⁶² Knoevenagel, Ger. pat., 162,281 (Frdl., 8, 1267).
 - ⁶¹ Dutt, J. Indian Chem. Soc., 1, 297 (1925); C. A., 19, 2475 (1925).
 - 44 Homolka, Ber., 18, 987 (1885); Claus and Wollner, Ber., 18, 1861 (1885).
- 4 Gabriel and Michael, Ber., 10, 1554 (1877); Gabriel and Neumann, Ber., 26, 952 (1893).

This acid undergoes a number of interesting transformations; on treatment with sodium methoride and subsequent warming with hydrochloric acid, carbon dioxide is evolved and 1,3-diketohydrindene is obtained. Cold aqueous alkalies open the lactone ring of phthalylacetic acid to form 2-carboxybenzoylacetic acid, which loses carbon dioxide readily to videl 2-acetylenzoic acid.

$$\begin{array}{c} \text{Co}_{\text{NaoCH}_1} \\ \text{Fhthalyi-} \\ \text{acetic acid} \\ \text{Noil} \\ \text{COCH}_2\text{Co}_1\text{H} \\ \text{COCH}_2\text{Co}_2\text{H} \\ \text{COCH}_3 \\ \text{COCH}_4\text{Co}_2\text{H} \\ \text{COCH}_4\text{COCH}_4\text{CO}_2\text{H} \\ \text{COCH}_4\text$$

Phthalic anhydride reacts with phenylacetic acid and sodium acetate, with evolution of carbon dioxide, to give benzalphthalide in 71-74% yields. 45

$$C_{\mathfrak{s}}H = C_{\mathfrak{s}}H_{\mathfrak{s}}CH_{\mathfrak{s}}CO_{\mathfrak{s}}H \to C_{\mathfrak{s}}H$$

Benzalphthalide is converted by sedium methoride into 1,3-diketo-2phenylhydrindene," and by concentrated aqueous alkalies into 2phenacetylbenzole acid. These transformations of the phthalic anhydride condensation products are useful preparative methods.

Acid Components

Although the Perkin reaction is considered to occur with the acid anhydride, there are numerous instances in which the resulting acrylic acid corresponds to the salt used and not the anhydride. Thus, sodium phenylacetate and acetic anhydride react with bensaldehydes to produce explenylcinnamic acids in excellent yields (Oglialoro's modification).* und oxecylaminoacetic acids react with bensaldehydes in the presence of acetic anhydride and sodium acetate at 100° to give derivatives of

⁴⁴ Gabriel, Ber., 18, 3470 (1885), Weiss, Org. Syntheses, 13, 10 (1933).

⁴⁷ Nathanson, Ber., 26, 2576 (1893); Eibner, Ber., 39, 2203 (1906).

α-acylaminocinnamic acids (azlactone synthesis). Owing to the exchange reactions that occur in mixtures of acids, salts, and anhydrides, even at 100°, the product will depend primarily upon the relative active-methylene reactivity of the various acid species present. For this reason it will be convenient in the present discussion to refer merely to the acid component that undergoes reaction, without necessarily specifying whether it is introduced as the free acid, salt, or anhydride.

The Perkin reaction is limited practically to acetic and monosubstituted acetic acids, RCH_2CO_2H , as two α -hydrogen atoms must be eliminated to form the α,β -unsaturation. Disubstituted acetic acids such as isobutyric acid give β -hydroxy- α,α -dialkylpropionic acids, but this reaction has little preparative significance as the Claisen or Reformatsky reaction (p. 8) is usually more satisfactory for such compounds; at higher temperatures the dialkylacetic acids yield dialkylstyrenes (p. 212). The present survey is restricted to monosubstituted acetic acids and related types, which are considered according to the nature of the substituent in the α -position.

Alkylacetic acids having a straight-chain alkyl substituent react quite readily with benzaldehyde to give α -alkylcinnamic acids in satisfactory yields.² Propionic, n-butyric,³ and n-caproic ¹⁶ anhydrides react with aromatic aldehydes at lower temperatures (100°) than acetic anhydride, and often give slightly higher yields. Palmitic anhydride and sodium palmitate are reported to give a 55% yield of α -n-tetradecylcinnamic acid.⁶⁹

Isocaproic acid appears to react normally 16 to form α -isobutylcinnamic acid, but isovaleric acid gives very small yields of the α -isopropyl derivatives. 10 Even at temperatures as low as 70° , a mixture of valeric anhydride, sodium valerate, and benzaldehyde evolves carbon dioxide, and isopropylstyrene is the main product; the same behavior occurs with p-anisaldehyde and with furfural. The decarboxylation is believed to occur at an intermediate stage since the α -isopropylacrylic acids, once formed, are stable above 100° . Cycloalkylacetic acids apparently have not been used in the Perkin reaction.

Crotonic anhydride, which is a vinylog of acetic anhydride, reacts with benzaldehyde in the presence of triethy-lamine (but not potassium crotonate) to give α -vinylcinnamic acid in 40% yield.²⁰

$$C_6H_5CHO + (CH_3CH=CHCO)_2O \xrightarrow{NEt_2} C_6H_5CH=CCO_2H$$
 $CH=CH_2OH$

⁶⁵ Erlenmeyer, Ann., 271, 164 (1892); 337, 265 (1904); see also Pl\u00f6chl, Ber., 16, 2815 (1883).

⁶³ Krafft and Rosins, Ber., 33, 3578 (1900).

The reaction is considered to involve a preliminary 1.4-enolization of the γ-methyl group to give the system CH -- CH-- CH-- C(OH)OAc, and subsequent addition of benzaldehyde at the a-position. Under similar conditions 8.8-dimethylaerylic anhydride gives a isopropenyleinnamic acid (38% yield): 70 the corresponding a-isoproperal derivatives have been obtained also from o-nitrobenzaldehyde, p-anisaldehyde pineronal cinnamaldehyde, and forfural.

Phenylacetic acid and other o-arylacetic acids react very satisfactorily with aromatic aldehydes to give o-aryleinnamic acids. Oglialoro 46 showed that sodium phenylacetate and acetic anhydride give a phenylcinnamic acid, and only a trace of cinnamic acid is formed. This modification, with subsequent refinements,* is a convenient preparative method as it obviates the necessity of isolating the arylacetic anhydride. The good yields obtained in this reaction are undoubtedly due to the ability of a arvl groups to enhance the active-methylene activity, as the order of reactivity of anhydride-salt combinations follows the sequence: α-aryl ≫ alkyl > hydrogen. n Tolylacetic acids 2 and other substituted arylacetic acids also give satisfactory yields.

Homologs of phenylacetic peid such as \$-phenylpropionic and \(\gamma \)-phenylbutyric acids are much less reactive than phenylacetic acid, and the Oglialoro medification gives poor yields owing to the formation of large quantities of cinnamic acid. 33. 14 The reaction is used nevertheless as a preparative method since the products cannot be synthesized conveniently in other ways. Sodium 8-phenylpropionate with benzaldehyde and acetic anhydride gives a-benzyleinnamic neid; " salts of p-chloro-, brome- iode- and dimethylamine-phenylpropionic acids give the corresponding substituted benzyl derivatives in low yields.24 Potassium r-phenylbutyrate with benzaldehyde and acetic anhydride (twelve days at 100°) gives a phenethylcinnamic acid in 14% vield.3

Phenylisocrotonic acid (styrylacetic or \$-benzalpropionic acid), a vinylog of phenylacetic acid, reacts satisfactorily when the sodium salt is used in combination with acetic anhydride. 25

 $C_1H_1CHO + C_2H_2CH = CHCH_2CO_2N_3 \xrightarrow{Ac_2O} C_2H_1CH_2 = CCO_2H$

CH=CHC.H.

^{*} For an example of the laboratory procedure see p. 253.

¹⁰ Ishikawa and Kato, Sci. Repts. Tokyo Bunrika Dangaku, I, 289 (1934), C. A., 28,

⁷¹ Bakuma, Gazz. chim stal., 31, 11, 77 (1991), Bakuma and Fisceman, ibid., 46, 1, 77 (1916).

[&]quot; Pschorr, Ber., 39, 3110 (1906).

⁷⁴ Rupe, Ann , 395, 106, 411 (1913).

¹⁴ Shonnee, J. Chem. Soc., 968 (1930).

N Thiele, Ann., 306, 154 (1899).

This reaction can be carried out in 20-25 minutes at 140°; the product is 1,4-diphenylbutadiene-2-carboxylic acid, which is structurally analogous to the acids obtained from crotonic and dimethylacrylic anhydrides (p. 224).

Malonic acid, owing to the powerful activating effect of two carboxyl groups on the same carbon atom, undergoes condensation with aliphatic and aromatic aldehydes under very mild conditions. In this particular case it is likely that the acid itself (in the enol form) reacts with the aldehyde, and the condensation can be effected satisfactorily under a wide variety of conditions. Undoubtedly the use of malonic acid is the best and most general preparative method for β -substituted acrylic acids. Until quite recently malonic acid has been a relatively expensive reagent and its use has been restricted largely to the less common aromatic aldehydes. It has also proved especially useful for aliphatic aldehydes and for various aromatic aldehydes that give poor results in the simple Perkin reaction (alkyl-, alkoxy-, dimethylamino-benzaldchydes, etc.).

The condensation of malonic acid with various aliphatic aldehydes (paraldehyde, ⁷⁶ propional dehyde, ⁷⁷ is obutyral dehyde, ⁷⁸ is ovaleral dehyde, ⁷⁹ etc.) was first effected in glacial acetic acid and a little acetic anhydride. Knoevenagel ⁶⁰ found that the reaction can be carried out with much better results using ammonia or primary or secondary amines (especially piperidine) as catalysts. Unfortunately neither of these modifications is a good preparative method in the aliphatic scries as mixtures of α,β - and β,γ -unsaturated acids are obtained. ⁵⁰ The most satisfactory method in the aliphatic (and aromatic) series is Doebner's modification ⁵² using pyridine, which has been studied by von Auwers. ⁵¹ He found that acetal dehyde gives exclusively crotonic acid (60% yield).

$$\text{CH}_3\text{CHO} + \text{CH}_2(\text{CO}_2\text{H})_2 \xrightarrow[20^9]{\text{C}_5\text{H}_2\text{N}} \text{CH}_2\text{CH} = \text{CHCO}_2\text{H} + \text{CO}_2$$

Propionaldehyde gives almost pure α,β -pentenoic acid, with only a trace of the β,γ -isomer; isobutyraldehyde, isovaleraldehyde, and n-heptaldehyde give almost entirely α,β -unsaturated acids. With n-heptaldehyde ⁵⁰ the β,γ -unsaturated acid amounts to 5–10%; the latter can be removed by stirring with 85% sulfuric acid at 80°, ⁵² which converts it to the γ -lactone (insoluble in sodium carbonate solution).

⁷⁵ Komnenos, Ann., 218, 149 (1883).

⁷⁷ Fittig, Ann., 283, 85 (1894).

⁷³ Braun, Monatch., 17, 213 (1896).

⁷¹ Schryver, J. Chem. Soc., 63, 1331, 1334 (1893).

⁶³ Zzar, Ber. Schimmel & Co. Ald. Gez., Jubilee Number, 299 (1929); C. A., 24, 2107 (1930).

²¹ von Auwers, Meisnner, Seydel, and Wissebach, Ann., 432, 46 (1923).

⁵² Shukow and Schestakow, J. Russ. Phys. Chem. Soc., 40, 830 (1905); Chem. Zentr., II 1415 (1905).

Acrolein ** and crotonaldehyde **. ** can be condensed with malonic acid in pyridine to give butadienerarboxylic acid and sorbic acid in satisfactory yields.

$$\text{CH}_1\text{CH} = \text{CHCHO} + \text{CH}_1(\text{CO}_1\text{H})_1 \xrightarrow{\text{C}_1\text{H}_2\text{N}} \text{CH}_1\text{CH} = \text{CHCH} = \text{CHCO}_2\text{H} + \text{CO}_2$$

Cinnamaldehyde reacts with malonic acid in the presence of ammonia or aniline, so or in the presence of pyridine; so so all the reaction is carried out at moderate temperatures cinnamalanionic acid is obtained, but at higher temperatures carbon dioxide is evolved and cinnamalacetic acid is produced.

Aromatic aldehydes react with malonic acid in the presence of ammonia and primary and secondary amines ⁶⁰ to give benzalmalonic acids, which, on heating, lose carbon dioxide to form β-arylacrylic acids.

$$C_4H_4CHO + CH_2(CO_2H)_2 \xrightarrow[ele]{\mathrm{NH}_2} C_4H_4CH = C(CO_2H)_2 \xrightarrow[Heat]{\mathrm{Heat}} C_4H_4CH = CHCO_4H$$

In the presence of large amounts of ammonia or methylamine the corresponding β -amino- β -arylpropionic acids are obtained in 50–60% yields, together with some of the cinnamic acid.⁴⁴

The arylacytle acids are obtained directly by the Doebner modification using pyridine as the solvent, and a small amount of piperidine. The reaction mixture is warmed for a short period on the steam bath and then refluxed for a few minutes. This is the outstanding preparative method for Berylacythe acids and often gives high yields of products which cannot be obtained by the ordinary Perkin reaction. Thus, 4-dimethylaminobenzaldehyde. The and 2,4-6-timethory-benzaldehyde. If do not react in the usual Perkin synthesis, but with malonie acid and pyridine they give the corresponding cinoamic acids in 65-85% and 70% yields, respectively. The Doebner method is also of great preparative value for hydroxycianamic acids, and it has been reported recently that the reaction can be carried out successfully with only a small amount of pyridine instead of using pyridine as a solvent. There is little doubt

^{k1} Riedel, Ann., 361, 89 (1908).

⁴¹ Rodionov and collaborators, Ber., 59, 2932 (1926); Arch. Pharm., 266, 116 (1928); J. Am. Chem. Soc., 51, 847 (1929)

Herrig, Wenzel, and Gehringer, Monatch., 24, S68 (1903).
 Vorsats, J. praki. Chem., [2] 145, 265 (1936)

W. Kurien, Pandya, and Surange, J. Indian Chem. Soc., 11, 823 (1934), C. A., 29, 3325 (1935). See also a series of papers by Pandya and collaborators, dealing with specific aldehydes:

⁽a) Saheylaldehyde: Proc. Indian Acad. Sci., 18, 440 (1935), C. A., 29, 3325 (1935), Chem. Zentr., II, 2362 (1935).

⁽b) Piperonal: Proc. Indian Acad. Scs., 2A, 402 (1935); C. A., 30, 1775 (1936), Chem Zentr., I, 4433 (1936).

that pyridinc exerts a definite eatalytic effect; substituted pyridinc bases differ quantitatively in their effectiveness.⁸⁷ Bachmann and Kloetzel ⁸⁸ have reported excellent yields of the corresponding acrylic acids from o-chlorobenzaldehyde and from several phenanthraldehydes (1-, 2-, 3-, and 10-), using malonic acid and a small amount of pyridine.

Fittig³ observed that sodium methylmalonate reacted with benzaldehyde in the presence of acetic anhydride to form α -methylcinnamic acid. No doubt other alkyl- and aryl-malonic acids would react with benzaldehyde to give α -substituted einnamic acids, but these reactions would be of little preparative value.

Fittig discovered that aromatic ¹³ and aliphatic ⁵⁴ aldehydcs react readily with sodium succinate and acetic anhydride at 100° , to give γ -phenyl- and γ -alkyl-paraeonic acids (p. 213) in satisfactory yields. These acids lose carbon dioxide on heating and form the β , γ -unsaturated acids, together with a small amount of the γ -butyrolactonc.

$$\begin{array}{c|c} \text{RCH} & \text{CHCO}_2\text{H} \\ \hline \mid & \mid & \text{RCH} & \text{CHCH}_2\text{CO}_2\text{H} + & \mid & \mid \\ \text{O} & \text{CH}_2 & & \text{O} & \text{CH}_2 \\ \hline \end{array}$$

This reaction affords a useful extension of the Perkin synthesis and has been used as a preparative method for a number of γ -substituted vinylacetic acids. Methylsuecinic acid gives a mixture of the isomerie α, γ -and β, γ -disubstituted paraconic acids. Phenylsuccinic acid and benzaldehyde react at 125° to give β, γ -diphenylvinylacetic acid. 90

⁽c) Anisaldehyde: Proc. Indian Acad. Sci., 4A, 134 (1936); C. A., 30, 8149 (1936), Chem. Zentr., I, 2767 (1937).

⁽d) p-Hydroxybenzaldehyde: Proc. Indian Acad. Sci., 4A, 140 (1936); C. A., 30, 8149 (1936), Chem. Zentr., I, 2768 (1937).

⁽e) m-Hydroxybenzaldehyde: Proc. Indian Acad. Sci., 4A, 144 (1936); C. A., 30, 8149 (1936), Chem. Zentr., I, 2768 (1937).

⁽f) o-Methoxy- and m-methoxybenzaldehyde: Proc. Indian Acad. Sci., 5A, 437 (1937); C. A., 31, 7412 (1937), Chem. Zentr., II, 3313 (1937).

⁽g) 2-Hydroxy-1-naphthaldehyde: Proc. Indian Acad. Sci., 6A, 181 (1937); C. A., 32, 1260 (1938), Chem. Zentr., I, 1356 (1938).

⁽h) 2,4-Dihydroxybenzaldehyde: Proc. Indian Acad. Sci., 7A, 381 (1938); C. A., 32, 7435 (1938), Chem. Zentr., II, 2736 (1938).

⁽i) p-Tolualdehyde: Proc. Indian Acad. Sci., 9A, 508 (1939); C. A., 33, 8589 (1939).

⁽j) 3,4-Dihydroxy-, 3-methoxy-4-hydroxy-, and 3,4-dimethoxybenzaldehyde: Proc. Indian Acad. Sci., 9A, 511 (1939); C. A., 33, 8589 (1939), Brit. Chem. Abstracts, AII, 478 (1939).

⁸⁸ Bachmann, J. Org. Chem., 3, 444 (1938); Bachmann and Kloetzel, J. Am. Chem. Soc. 59, 2209 (1937).

⁵⁹ Fittig, Ann., 255, 5, 7, 108, 126, 257 (1889).

⁵⁰ Fichter and Latzko, J. prakt. Chem., [2] 74, 330 (1906).

$$\begin{array}{c} C_{e}H_{a}CHO + C_{e}H_{4}CHCo_{2}Na \xrightarrow{A \circ gO} C_{e}H_{g}CH = CCH_{2}CO_{2}H + CO_{2} \\ \downarrow & \downarrow & \downarrow \\ CH_{2}Co_{2}Na & C_{e}H_{e} \end{array}$$

Phenylsuccinic acid and cinnamaldehyde sigive only a small amount of the vinylogous unsaturated acid as the latter is transformed mainly into 2.5-diphenylphenol.

Glutaric acid reacts with benzaldehyde to form only a trace of δ-phenyl-γ,δ-pentenoie acid (C₆H₅CH=CHCH₂CH₂CO₂H),² but phenylglutaric acid reacts more satisfactorily and gives γ,δ-diphenyl-γ,δ-pentenoie acid ²⁸

The Perkin reaction is unsuitable for the direct preparation of a-halogenated cinnamic acids. When benzaldehyde is heated with sedium chloroacetate and acetic anhydride only a trace of a-chlorocinnamic acid is formed.** Sodium bromoacetate ** and fluoroacetate ** under similar conditions give none of the corresponding a-halogenated cinnamic acids. a-Bromocinnamic acid (in a variety of crystalline form) can be obtained by the action of bases on the bromide of cunnamic acid under carefully controlled conditions; aqueous sodium carbonate or acctate converts the dibromide largely to β-bromostyrens.

a-Phenoxy- and cresoxy-cinnamic acids can be prepared by heating the sodium salts of arylexyacetic acids with benzaldehyde and acetic anhydride, but some cinnamic acid is formed also. The parent comnound, a-hydroxycinnamic acid, is the engl form of phenylumynic acid.

$$C_6H_6$$
- CH = C - CO_2H $\rightleftharpoons C_6H_6$ - CH_7 - CO - CO_2H

Owing to this relationship certain derivatives of e-thioleinnamic acid (benzalrhodanine, etc.)** and e-scylaminocinnamic acid (azlactones, etc.) can be hydrolyzed to give phenylpyruvic acid, and this forms an elegant preparative method for arylpyruvic acids ** and related compounds.**

Several derivatives of a-thioleianamic acid can be obtained from the corresponding a-thiolacetic acids. Sodium thiodiglycolate reacts with

- M Fichter and Grether, Ber., 36, 1407 (1903).
- Pittig, Ann., 282, 334 (1894).
- Fichter and Merkens, Ber., 34, 4177 (1981).
 Plochl, Ber., 15, 1945 (1882).
- 14 Michael, J. proki. Chem., [2] 40, 64 (1889).
- ** Snarts, Bull. soc. chim , [4] 25, 325 (1919).
- " Oghaloro, Gazz. chim. stat., 10, 493 (1880), 20, 505 (1890).
- M Granacher, Hels. Chim. Acta, 5, 610 (1922).
- " Buck and Ide, Org. Syntheses, 15, 33 (1935), Herbet and Shemin, ibid., 19, 77 (1939)

two molecules of benzaldehyde in the presence of acetie anhydride to give α -thio-bis-einnamie acid, and no cinnamie acid is formed under these eonditions.¹⁰⁰

$$C_6H_6CHO + S(CH_2CO_2Nn)_2 \xrightarrow{\Lambda e_2O} S \begin{pmatrix} -C - CO_2H \\ \parallel \\ CHC_6H_5 \end{pmatrix}_2$$

The most significant reaction of this type for preparative purposes is the condensation of cyclic sulfur compounds, such as rhodanine (and related heterocyclic derivatives), with aromatic aldelydes. This condensation can be effected readily under various conditions as the methylene group of rhodanine is quite active; * excellent yields are obtained using a combination of glacial acetic acid and sodium acetate.¹⁰¹

The resulting derivatives are useful intermediates for the preparation of arylthiopyruvic acids, ⁹⁸ β-arylalanines, ⁹⁸ arylacetonitriles, arylacetic acids, β-arylethylamines, etc. ^{101, 102} These reactions have been particularly useful in the furan series ^{98, 102} and for alkoxyphenyl compounds. ¹⁰¹ Furfural has been converted to 2-furanacetic acid ¹⁰² in an over-all yield of 73% by the following typical series of transformations (five steps).

It is difficult to find another series of reactions that gives such uncommonly good yields. It is of interest to note that the process does not require strong mineral acids at any stage and consequently is well adapted for use with acid-sensitive groups.

^{*} For a survey of earlier references to these condensations see Grānacher, reference 98 100 Loeven, Ber., 18, 3242 (1885); see also Hinsberg, J. prakt. Chem., [2] 84, 192 (1911)

¹⁰¹ Julian and Sturgis, J. Am. Chem. Soc., 57, 1126 (1935).

¹⁰² Plucker and Amstutz, J. Am. Chem. Soc., 62, 1512 (1940).

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A large number of derivatives of aminoacetic acid undergo condensation with benzaldehyde and other aldehydes of aromatic type, in essentially the same manner as rhodanine. The most familiar example is the condensation of hippuric acid with benzaldehyde in the presence of acetic anhydride and sodium acetate (Erlenmeyer's azlactone synthesis). ⁴⁵

$$\begin{array}{c} C_4\Pi_4CHO + C\Pi_4CO_2\Pi & \xrightarrow{A_{P,O}} & C_4\Pi_4CH = C & & C_4\Pi_4CH = C & & C_4\Pi_4CH = C & & C_4\Pi_4 & & C_4\Pi$$

The yields of atlactones (substituted oxazolones)* from hippuric acid are usually quite good (62-64% with benzaldehyde,1¹⁰ 69-73% with 3,4-dimethoxybenzaldehyde ***), and similar or somewhat better results are obtained when accturic acid is used (74-77% yield of azlactone from benzaldehyde) ***

Mild hydrolysis of the azlactones with alkalies gives the a-acylaminocinnamic acids (II), and further hydrolysis yields the arylpyruvic acids (III), the 19

For this type of reaction the α -acetamido compounds ¹²⁸ are preferable to the α -benzamidocinnamic acids, as the former are less resistant to hydrolysis ¹⁷⁸ in his is particularly true for atlactones derived from α -nutro-benzaldehydes, which undergo a vanety of side reactions on varning with alkalics. ¹²⁸ The arphynutic acids are useful intermediates in synthetic work; on oxidation with hydrogen perovide they give anylacetic acids in good yields. ¹⁷⁸ The atlactones and α -acylaminocinnamic acids can be transformed into β -arg- α -ammonpropionic acids by warning with phosphorus and hydriodic acid, ¹⁸⁸ or by catalytic reduction and subsequent hydrolysis. ¹⁸⁹

^{*} In Chemical Abstracts and Besisten's Hausbuck the salactone (I) from hippure acid and benealdshyde is named 2-phenyl-4-beneal-5-oxacolone, that from accture acid is 2-methyl-4-beneal-5-oxacolone. In British usage the former (I) is called 5-keto-2-phenyl-4-benzylidene-4-5-dihydrofusatole.

¹⁶¹ Gillespie and Soyder, Org. Syntheses, 14, SI (1934).

¹⁰ Buck and Ide, Org. Syntheses, 13, 8 (1933), see also thid., 15, 31, 33 (1935).

¹⁰¹ Herbst and Shemin, Org. Syntheses, 19, 1 (1939), see also pp. 67 and 77.

¹⁰⁰ Burton, J. Chem. Soc., 1265 (1935); 402 (1937).

Erlenmeyer found that N-phenylglycine (i.e., its acetyl derivative, which has no hydrogen on the nitrogen atom) does not give an azlactone, but he showed that creatine can be condensed with benzaldehyde in the presence of acetic anhydride and sodium acetate. Under improved conditions ¹⁰⁷ an 80% yield of N-acetyl-5-benzalcreatine (IV) is ob-

$$\begin{array}{c|c} C_6H_5CH=C & CO & \\ \hline & & & \\ CH_2N & NH & \hline \\ & & & \\ CH_3N & NH & \hline \\ & & &$$

tained, and this on reduction and hydrolysis can be transformed into N-methylphenylalanine (V); this affords a useful general method for N-methyl derivatives of β -substituted alanines.^{107, 108}

Hydantoin condenses with a variety of aromatic aldehydes (including anisaldehyde, piperonal, furfural, etc.) in the presence of acetic acid, sodium acetate, and a little acetic anhydride. The corresponding 5-benzalhydantoins (VI) are obtained in good yields (70–85%) and are useful intermediates for amino acid syntheses. Similar condensation

products (VII) can be obtained from acylthiohydantoins ¹⁰⁹ under similar conditions. It has been reported recently that 92–98% yields of 1-acetyl-5-benzal-2-thiohydantoins (VII) are secured from acetylthiohydantoin by using pyridine and a trace of diethylamine or pyridine, ¹¹⁰ but this procedure gives inferior yields (30–40%) with hydantoin itself.

Cyanoacetic acid reacts readily with aromatic aldehydes to give α -cyanocinnamic acids, which can be decarboxylated by heating to give the β -arylacrylonitriles.¹¹¹

¹⁰⁷ Nicolet and Campbell, J. Am. Chem. Soc., 50, 1155 (1928).

¹⁰⁵ Deulofeu and Mendivelzua, Ber., 68, 783 (1935).

¹⁰⁹ Wheeler and Hoffman, Am. Chem. J., 45, 369 (1911); see also Wheeler, Nicolet, and Johnson, ibid., 46, 471 (1911).

¹¹⁹ Boyd and Robson, Biochem. J., 29, 542 (1935); C. A., 29, 5094 (1935).

¹¹¹ Fiquet, Bull. soc. chim., [3] 7, 11 (1892); Ann. chim, [6] 29, 433 (1893).

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The α-cyanocinnamic acids are prepared conveniently by using an aqueous solution of sodium cyanoacetate obtained from sodium cyanide and chloroacetic acid. The α-cyanocinnamic acids cannot be used as intermediates for preparing benzalmalonic or cinnamic acids since they are resistant to hydrolysis by acids and are cleaved into benzaldehyde and malonic acid by strong alkalies. The addition of sodium cyanide to ethyl α-cyanocinnamate and subsequent hydrolysis with acids gives phenyl-urcinic acid in 90-93% yields. The addition of ethyl malonate to ethyl α-cyanocinnamate leads in a similar way to α-phenylglutaric acid in 78-05% yields.

The condensation of benzyleyanide with aromatic aldehydes leads directly to the nitriles of c-aryleinnamic acids, C₂H₂CH=C(C₆H₂)CN, ¹⁵ which have limited application in synthetic work.

Comparison with Other Synthetic Methods

From the standpoint of its application in organic synthesis the Perkin reaction is used most generally for the preparation of \$\textit{\textit{\textit{parable}}} and acsubstituted.\$\textit{\textit{parable}} and its Two other methods of very general utility are available for the same purpose—the Claisen condensation of aldelyades with esters and the Reformatsky reaction. For the purpose of this discussion the condensations of malonic acid in the presence of anumonia and primary or secondary amines will be designated as the Knoevenagel modification *of the Perkin reaction, and the use of malonic acid in pyridine (usually with a httle paperidine added) will be designated as the Doebner modification.† A general comparison of these reactions may be made for a simple example, such as the preparation of cinnamic acid from benzaldehyde (see also p. 8)

Perkin: Actic anhydridic potassium acetate; five hours' heating

at 175-180°; yield, 55%.

*The term Knoevenage's reaction is used very broadly to include the condensation of

^{*}The term Knoevenagel reaction is used very broadly to include the condensation of extension in the properation of the condensation of earthough components in the presence of ammonia or primary or accordary amuses.

[†] The term Doebner reaction is often used for the synthesis of α-alkyl- and α-arylcinchomine acids from aromatic amores, althodycies, and pyrurue scal. ¹¹¹ Lapsworth and McTae, J. Chem. Soc., 131, 1699 (1932), Lapsworth and Baker. Org.

¹³ Lapworth and McRae, J. Chem. Soc., 131, 1699 (1932), Lapworth and Baker, Org. Symboles Coll. Vol., I, 175 (1932).

¹¹⁴ Lapworth and Baker, Org. Syntheses Coll Vol . I, 440 (1932).

¹¹⁴ Mansks, J. Am. Chem. Soc., 53, 1106 (1931).

¹⁰ Frost, Ann. 250, 157 (1889); Walther, J. prait. Chem., [2] 53, 454 (1896); Brand Löhr, ibid. [2] 109, 365 (1925).

Knoevenagel: Malonic acid; ammonia, piperidine, or diethylamine, alcohol as solvent; two to four hours' heating at 100°; yield, 70-80%.

Doebner: Malonic neid; trace of piperidine; pyridine as solvent; one to two hours' heating at 100°; yield, \$0-90%.

Claisen: Ethyl acetate, absolute; metallic sodium and a trace of alcohol; excess of ethyl acetate serves as solvent; two hours at 0-5°; vield, 68-74%.¹¹⁶

Reformatsky: * Ethyl bromoacetate; metallic zinc; benzene as solvent; one to two hours at 100° , followed by heating and distillation (to delay-drate intermediate β -hydroxy ester); yield, 50-60%.

In the Claisen reaction the product is an ester, which can be saponified readily to obtain the acid; in the Reformatsky reaction, the intermediate β -hydroxy ester is subjected to dehydration and the resulting cinnamic ester distilled and saponified.

C₆H₅CHO + CH₂CO₂C₂H₅
$$\xrightarrow{N_3}$$
 C₆H₅CH=CHCO₂C₂H₅ ÷ H₂O
(Claisen reaction)

$$C_{\varepsilon}H_{s}CHO + B_{r}CH_{2}CO_{2}C_{2}H_{5} \xrightarrow{Z_{2}} C_{\varepsilon}H_{s}CHOHCH_{2}CO_{2}C_{2}H_{5}$$

$$\downarrow H_{ext}$$

$$C_{\varepsilon}H_{s}CH = CHCO_{2}C_{2}H_{5}$$

(Reformatsky reaction)

The direct formation of an ester may be advantageous in many instances, as the purification of an ester by distillation is likely to be more convenient and less wasteful of material than recrystallization of the solid acid. Moreover, the esters are often desired in preference to the free acids for use in subsequent transformations, such as conversion to amides, catalytic hydrogenation, and formation of addition or substitution products.

The Perkin reaction is particularly well suited for reactions involving nitrobenzaldehydes and halogenated benzaldehydes, since especially high yields are obtained with these compounds and these types of substituents are unfavorable for the Claisen or Reformatsky reactions. Benzaldehydes containing a free phenolic group are likewise unsuited for the Claisen or Reformatsky reaction but may be protected by alkylation or acetylation. In the Perkin reaction o-hydroxybenzaldehydes give coumarins; the m- and p-hydroxy compounds yield the corresponding acetoxycinnamic acids, which can be hydrolyzed readily with alkalies. The Doebner modification is suitable for hydroxy compounds and gives

^{*} See Chapter 1.

¹¹⁶ Marvel and King, Org. Syntheses Coll. Vol., I, 246 (1932).

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especially good results if the reaction is carried out by long standing at room temperature. 46

The Claisen reaction is definitely superior to the ordinary Perkin reaction for alkylbenzaldehydes, alkoybenzaldehydes, and p-dimethyl-aminodenzaldehyde. These types give 60-85% yields of the corresponding cinnamic esters in the Claisen reaction, and similar good yields in the Dochner modification of the Perkin reaction; the Knoevenngel modification is satisfactory also for such preparations. 2,4,6-Trimethyl-cinnamic acid is obtained only in traces in the usual Perkin reaction, but the ethyl ester can be prepared in 70% yield by the Claisen method."

The Doebner modification is rapid and convenient, and for large-scale preparations is less hazardous than the Claisen reaction. A large quantity of pyriding is required, and it must be anhydrous for maximum yields. A technical fraction of pyridine bases (b.p. 120-160?), after redistillation and thorough drying, gives as good results as pure pyridine; recent studies indicate that the pyridine bases can be used in stoichiometric quantities ¹¹ and even in catalytic amounts. ¹² The Knoevenagel modification is simpler from the standpoint of solvent required, as alcohol is a satisfactory medium. Neither the Doebner nor the Knoevenagel modification is used for e-substituted einnamic acids as the requisite monossubstituted malonic acids are not readily accessible.

A satisfactory synthesis of substituted cinnamic acids from the corresponding benzyl halides has been developed by von Braun and Nelles. ¹¹⁸ The benzyl halide is converted to the corresponding malonic acid in the conventional way; the resulting Barylmalonic acid is then brominated, decarbovylated, and treated with alkalı.

$$RCH_2Br \rightarrow RCH_2CH(CO_2H)_2 \xrightarrow{Br_2} RCH_2CBr(CO_2H)_2 \xrightarrow{Heat} RCH_2CHBrCO_2H \xrightarrow{NaOR} RCH=CHCO_2H$$

This method is not suitable for aliphatic or alicyclic compounds but gives good over-all yields with a variety of substituted benzyl halides. The advantage of this synthesis over the Perkin or Claisen reaction less in the circumstance that the benzyl halides are often more readyl accessible than the corresponding benzaldelydes.

o-Arylcinnatus acids are prepared most readily by the Perkin reaction, but good yields of the esters can be obtained in the Claisen reaction. e-Alkylcinnanic acids are obtained readily by the Perkin reaction but sometimes more conveniently by the Claisen or Reformatsky reaction. Another method of preparative value involves the condensation of ben

Dalal and Dutt, J. Indian Chem. Soc. 9, 309 (1932), C. A., 27, 279 (1933).
 Yon Braun and Nelles, Ber., 66, 1464 (1933).

zaldehyde with alkyl derivatives of acetone, and oxidation of the resulting benzalacetones with sodium hypochlorite.¹¹⁷

This method has been used for α -n-propyl-, n-butyl-, and n-amyl-cinnamic acids. Benzalacetone itself gives cinnamic acid by hypochlorite oxidation, and a limited number of ring-substituted cinnamic acids have been prepared by this method.

The Doebner modification appears to be the best general method for the preparation of β -alkylacrylic acids and can be used to a limited extent for β , β -dialkylacrylic acids. The acids obtained in this way are less likely to be contaminated with the isomeric β , γ -unsaturated acids.

The Reformatsky reaction is the only one of the reactions that is suited for the direct preparation of β , β -diarylacrylic acids, as benzophenone and its derivatives will react with bromoacetic esters and zinc but will not take part in the Perkin or Claisen reaction.

SELECTION OF EXPERIMENTAL CONDITIONS

A number of studies have been made of factors influencing the yields in the Perkin reaction, but it is difficult to draw any broad generalizations. In many of the preparations described in the literature the proportions of reactants and the general procedure have been essentially those used by Perkin: a mixture of two parts of the benzaldehyde with one part (by weight) of freshly fused sodium acetate and three parts (by weight) of acetic anhydride is heated for about eight hours at 175–180°. These proportions correspond, in the case of benzaldehyde, to about 1.5 moles of acetic anhydride and 0.65 mole of sodium acetate. Meyer and Beer 22 reported that 2.1 moles of acetic anhydride and 0.7 mole sodium acetate per mole of aldehyde gave the best results for a group of substituted aldehydes.

Recent work 27 indicates that a slightly larger proportion of sodium acetate, about 1 mole instead of 0.65–0.7 mole, gives a small improvement in the yields (5–10%). Further increases in the amount of sodium acetate, up to 2 moles, have little effect, but beyond this point the yields fall off. There is generally but little advantage in using more than 1.5 moles of acetic anhydride per mole of aldehyde; the use of 2 moles of anhydride increases the yield only a small amount (1–3%), and a large excess is deleterious. The use of an indifferent solvent such as toluene

¹¹¹ Ger. pai., 21,162 (1882) (Frdl., 1, 28); see also reference 131, p. 243.

or nitrobenzene causes a marked drop in the yield and can impede the reaction completely. The addition of a small amount of pyridine (8 drops for 0.2 mole benzaldehyde) raises the yield of cinnamic acid from 50-60% to 80-85%.

It is "ported?" that the yield of eimamic acid is increased (using the proportions of Mcyer and Beer) by prolonged heating at 180°. The yields were as follows: heating two hours, 6%; four hours, 21%; is hours, 35%; cight hours, 45%; ten hours, 52%; fourteen hours, 61%; thenty-four hours, 72%; ciffy hours, 65%; one bundred hours, 72%. Although the yields may be increased in this way with certain aldelydes, with others better yields are obtained by shorter periods of heating and at lower temperatures. In general a period of seven to clight hours' heating at 170-180° is adequate when sodium acetate is used. A period of three to five hours' heating at 140-160° may be sufficient if potassium acetate is used, and better yields are secured in this way with some aldehydes.

Meyer and Beer ** studied the influence of a series of metallic acctates on the yields of various cinnamic acids and observed that potassium acctate gave a definite improvement over sodium acctate (34% yield as against 45%, with benshlebyde). With o-thlorobensaldehyde and various metallic acctates, using 21 moles anblydride and 0.7 mole acctate (cight hours at 180°), the yields were: lithium, 58%; sodium, 71%; potassium, 75%; rubsdium, 85%; magnesium, 0%; calcium, 8%; barium, 3%: copper, 35°, tede, 70%; mercury, 37%.

Kalini if earried out an extensive study of various factors influencing the yields in the Perkin reaction.* He found that tertiary amines catalyze the formation of cinnamic acid from bearnidehyde and acetic anhydride, in the absence of metallic acetates, and that their activity increases with the basic strength of the amine. Likewise, there is an optimum ratio of anine to acid anhydride; with triethylamine this is about one-third mole, but for weaker base a larger proportion is required. Benzaldehyde, acetic anhydride (1 mole), and triethylamine (0.33 mole), heated at 180° for eight hours, gave a 29% yield of cinnamic acid; the same amount of pyridine gave only 1% yield. These amines were slightly more effective with propionic than with acetic anhydride. A mixture of benzaldehyde (1 mole), heavylacetic anhydride (5 moles), acetic anhydride (4 moles), and pyridine (2 moles) gave a 95% yield of explenylcinnamic acid after five hours' heating at 150°.

Kalnin ¹³ also found that metallic salts other than acetates can act as catalysts in the Perkin reaction The following yields of cinnamic acid were obtained using benzaldchyde (1 mole), acetic anhydride (1.5

^{*} Kalnin's paper also includes a survey and critical review of earlier work in the field.

moles), and various metallic salts (0.65 mole-equivalent), with eight hours' heating at 180°.

Potassium acetate	72%	Potes-ium sulfite	32%
Potassium carbonate	59%	Tripotassium phosphate	2076
Sodium carbonate	40%	Pota-dum sulfide	8%
Sodium acetate	33%	Potas-ium cynnide	017
Tri-odium pho-phate	35%	Potaium ioriide	000

The effect of the duration of heating (at 180°) was studied for three of these catalysts, and the following yields were obtained.

	ONE-FOURTH HOUR	One Horn	Four Hours	Eight Hours
Potassium carbonate	34%	4076	527c	5976
Sodium carbonate	377	14%	27%	4076
Sodium acetate	0%	256	20%	30.5

Kalnin's results indicate that potassium carbonate may be substituted advantageously for sodium acetate but that it is not quite so effective as potassium acetate.

Chappell is investigated the duration of heating when potassium acetate is used, and compared three aldehydes under similar conditions (1.5 moles anhydride and 0.63 mole potassium acetate, at 180°). The following yields were obtained.

	Two Hours	Forn Horns	Six Horris	Eight Hours
Benzaldehyde	52%	55%	55°%	60%
Anisaldehyde	30%	35%	3 9%	20%
Furfural	55%	49%	4076	25%

A parallel series of experiments using sodium acetate showed that the yields increased steadily up to eight hours' heating. It is clear that the optimum conditions with potassium acetate are likely to be quite dissimilar for different types of aldehydes. For furfural the most favorable results were obtained with four to five hours' heating at 150°, or six to seven hours at 140°; in when potassium acetate was used the addition of pyridine did not improve the yield.

In the presence of the most active acetates cinnamic acid is formed slowly at 100°; the following yields were obtained by boiling for one minute to dissolve the salt,* and then heating at 100° for sixteen hours: 12° potassium acetate, 2%; rubidium, 19%; cesium, 20%; tetraethylam-

^{*}The solubility of the metallic acetates in the reaction mixture is an important factor and Kalnin attributes the results of Meyer and Beer, in part, to the low solubility of certain of the salts, for example, lithium acetate. Kalnin's rate studies with the aikali carbonates suggest that these bases neutralize the acetic acid formed during the reaction and thereby offset its retarding effect.

¹²¹ Chappell, Thesis, Cornell University, 1933.

¹²¹ Johnson, Org. Syntheses, 20, 55 (1949).

monium, 18%; thallous, 14%; lead, 0%. Rubidium and cesium salts are too rare to be used for preparative purposes, but these results suggest that quaternary ammonium salts might be good catalysts under appropriate conditions.

Michael observed that free acetic acid has a retarding effect on the formation of cinnamic acid. This is readily understandable in terms of the current theory that the reaction involves enolization of the anhydride, since acetic acid would suppress the enolization. Kalnin obtained the following yields of cinnamic acid when increasing amounts of glacial acetic acid were added to the usual reaction mixtures and the reactions were carried out at 180° for eight hours.

ACETATE USED	MOLES OF ACETIC ACID ADDED AND YIELDS				ELDS
	None	0 65 mole	185 moles	\$1 moles	4.8 moles
Potassium	72%	51%	21%	6%	2%
Sodium	39%	32%	17%		1%

The effect of acetic acid depends upon the degree of activity of the reacting components o-Chlorobenzaldelyde reacts readily with a mixture of potassium acetate and glacial acetic acid to give o-chlorobenzanic acid in 70% yield; with a less reactive salt, sodium acetate, only half of the aldebyde undergoes reaction and the yield wonly 24%. With compounds having a very active methylene group (malonic acid, cyanoacetic acid, rhodanine, 100 hydantom, 100 tect,), excellent yields of condensation products can be obtained in the presence of glacial acetic acid.

The unfavorable effect of acetic acid is reduced in the customary procedures for the Perkin reaction by using an air-cooled condenser, and at the temperatures employed the acetic acid distils out of the reaction mixture. This means of overcoming the retarding effect of the acetic acid formed in the reaction is of considerable importance with benzaldehyde and less reactive aldehydes. It is quite likely that discrepancies in yields reported in the literature are due in large measure to variations in the extent of removal of acette acid.

The effect of various factors on the reaction of phenylacetic acid (or anhydride) with o-nitrobenzaldchyde has been studied exhaustively by Bakunin and Peccerillor "They obtained the following yields of ornitrophenylcinnamic acid when a standard reaction mixture (1 mole aldelyde, 1 mole phenylacetic acid, 3 moles acette anhydrade, 1 mole metallic salt or oranin base) was beated for twelve hours at 109°.

Sodium acetate	68%	Trimethylamine	897
Sodium benzoate	60%	Triethylamine	95%
Potassium acetate	70%	Tripropylamine	98%
Ethanolamine	356	Trascemylamine	8756
Pyridine	33%	No salt or amine	0%

Thus, with two very reactive components, the tertiary amines proved to be very effective catalysts, whereas Kalnin found that triethylamine gives only a 29% yield of cinnamic acid with benzaldehyde and acetic anhydride. In another series of experiments, using phenylacetic anhydride, Bakunin and Peccerillo 12 obtained the following yields.

Rubidium acetate	8956	Pyridine	4250
Potassium acetate	78°6	Trimethylamine	85%
Sodium acetate	72%	Triethylamine	8750
Lithium acetate	3450	Diethylamine	8%
Barium acetate	27%	Piperidine	23%
Without any salt or	•	Aniline	0%
amine	6%	Ammonia	0%

These workers found that acetic anhydride can be replaced by propionic, butyric, or valeric anhydride, but benzoic anhydride gave low yields of o-nitrophenylcinnamic acid. Inorganic dehydrating agents such as phosphorus pentoxide and anhydrous calcium chloride were ineffective. Likewise, ethyl phenylacetate could not be substituted for phenylacetic acid (or anhydride).

USE OF THE PERKIN REACTION IN SYNTHESIS

The Perkin reaction and related condensations afford a means of transforming an aromatic aldehyde group into a variety of side chains. The corresponding reactions can be used only to a limited extent with aliphatic aldehydes (and a few ketones) but are nevertheless of some preparative value in the aliphatic series. The types of compounds that will participate in these reactions have been reviewed in considering the scope of the reaction (pp. 217–233). The following brief summary indicates the types of compounds that can be obtained directly by means of the Perkin reaction in its varied forms.

a, \beta-Unsaturated Acids

RCH=CHCO₂H. \$\beta\$-Arylacrylic acids are prepared by the usual Perkin reaction, or by the Knoevenagel and Doebner modifications using malonic acid. 1-Naphthaldehydes, 2-furanaldehydes, and 2-thiophenealdehyde may be used instead of benzaldehyde. \$\beta\$-Alkylacrylic acids can be prepared from aliphatic aldehydes and malonic acid, preferably by the Doebner modification.

R₂C=CHCO₂H. β , β -Diarylacrylic acids cannot be prepared by the Perkin reaction; the β , β -dialkylacrylic acids can be obtained from dialkyl ketones and malonic acid, preferably by the Doebner modification.

RCH=CCO2H, a-Alkyl- and a-aryl-cinnamic acids are prepared

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readily by the Perkin reaction from benzaldehydes and substituted acetic acids. a-Vinvlcinnamic acids may also be prepared (see below).

Other Upsaturated Acids

RCH=CHCH2CO2H. 7-Alkyl and 7-aryl derivatives of vinylacetic acid can be obtained by using sodium succinate and acetic anhydride in the Perkin reaction. Under mild conditions (120°) the intermediate paraconic acids can be obtained (Fittig's modification). β,γ-Dienbstituted derivatives are obtained by using sodium methyl- or phenyl-succinate. It is reported that the Knoevenagel modification, using malonic acid and amines, often gives mainly β,γ -unsaturated acids when aliphatic aldehydes are used.30

RCH-CHCH2CH2CO2H. The reaction of sodium glutarate with benzaldehyde gives very low yields of γ-benzalbutyric acid (R = Calla). Sodium α-phenylglutarate reacts more satisfactorily and gives γ,δ-di-

phenyl-y-pentenoic acid.

RCH-CHCH-CHCO₂H. Butadiene-1-carboxylic acid (R = II) and sorbic acid (R = CII₃) can be prepared from aerolein and crotonaldehyde, respectively, using the Doebner modification. 4-Phenylbutadiene-1-carbovylic acid ($R = C_0H_0$) can be obtained from einnamaldehyde in the usual Perkin reaction, and also by the Knoevenagel or Doebner modification.

RCH-CHCH-CCO2H. 1-Alkyl and 1-aryl derivatives of 4-phenyl-

butadiene-1-carboxylic acid are prepared from cinnamaldehyde and substituted acctic acids in the usual Perkin reaction

RCH=CCH=CH2. 1-Phenylbutadiene-2-carboxyle acid is obtained

by condensation of benzaklehyde with crotonic anhydride in the presence of triethylamine * The corresponding 3-methyl homolog is obtained by using β-methylerotonic anhydride.**

RCH=CCH=CHR. 1,4-Diarylbutadiene-2-carboxylic acids are ob-

tained by condensing benzaldehydes with β-benzalpropionic acid.122

¹⁹ Thiele, Ann., 306, 154 (1990); Schenck, J. pratt. Chem., 12 141, 299 (1934).

Thus, with two very reactive components, the tertiary amines proved to be very effective eatalysts, whereas Kalnin found that triethylamine gives only a 29% yield of einnamic acid with benzaldehyde and acetic anhydride. In another series of experiments, using phenylacetic anhydride, Bakunin and Peccerillo 19 obtained the following yields.

Rubidium acetate	80%	Pyridine	42%
Potassium acetate	78%	Trimethylamine	85%
Sodium acetate	72%	Tricthylamine	87%
Lithium acetate	34%	Diethylamine	8%
Barium acetate	27%	Piperidine	23%
Without any salt of	r	Aniline	0%
amine	6%	Ammonia	0%

These workers found that acetic anhydride can be replaced by propionic, butyric, or valeric anhydride, but benzoic anhydride gave low yields of o-nitrophenyleinnamic acid. Inorganic debydrating agents such as phosphorus pentoxide and anhydrous calcium chloride were ineffective. Likewise, ethyl phenylacetate could not be substituted for phenylacetic acid (or anhydride).

USE OF THE PERKIN REACTION IN SYNTHESIS

The Perkin reaction and related condensations afford a means of transforming an aromatic aldehyde group into a variety of side chains. The corresponding reactions can be used only to a limited extent with aliphatic aldehydes (and a few ketones) but are nevertheless of some preparative value in the aliphatic series. The types of compounds that will participate in these reactions have been reviewed in considering the scope of the reaction (pp. 217–233). The following brief summary indicates the types of compounds that can be obtained directly by means of the Perkin reaction in its varied forms.

α,β-Unsaturated Acids

RCH=CHCO₂H. β-Arylaerylic acids are prepared by the usual Perkin reaction, or by the Knoevenagel and Doebner modifications using malonic acid. 1-Naphthaldehydes, 2-furanaldehydes, and 2-thiophenealdehyde may be used instead of benzaldehyde. β-Alkylaerylic acids can be prepared from aliphatic aldehydes and malonic acid, preferably by the Doebner modification.

R₂C=CHCO₂H. β,β -Diarylaerylic acids cannot be prepared by the Perkin reaction; the β,β -dialkylaerylic acids can be obtained from dialkyl ketones and malonic acid, preferably by the Doebner modification.

RCH=CCO₂H. α-Alkyl- and α-aryl-cinnamic acids are prepared R

readily by the Perkin reaction from benzaldchydes and substituted acetic acids. \(\alpha\)-Vinyleinnamic acids may also be prepared (see below).

Other Uncaturated Acids

RCH=CHCH₃CO₂H. γ -Alkyl and γ -aryl derivatives of vinylacetic acid can be obtained by using sodium succinate and acetic anhydride in the Perkin reaction. Under mild conditions (120°) the intermediate paraconic acids can be obtained (Fittig's modification). β ₁ γ -Disubstituted derivatives are obtained by using sodium meltily- or phenyleuccinate. It is reported that the Knoevenagel modification, using malonic acid and amines, often gives mainly β ₁ γ -unsaturated acids when alliphatic aldehvides are used ³⁹

RCH=CHCH₂CH₂CO₂H. The reaction of sodium glutarate with benzaldehyde gives very low yields of \(\gamma\)-benzalbutyric acid (\(\text{R} = \mathbb{C}_0^2 \)-\(\text{R}_0^2\). Sodium \(\sigma\)-benylclutarate reacts more satisfactorily and gives \(\sigma\)-\(\text{R}_0^2\).

phenyl-y-pentenoic acid.

RCH—CHCH=CRCO₂H. Butadiene-1-carboxylic acid (R = H) and sorbic acid ($R = CH_3$) can be prepared from acrolein and croton-aldehyde, respectively, using the Doebner modification. 4-Phenyl-butadiene-1-carboxylic acid ($R = C_6H_3$) can be obtained from enamaldehyde in the usual Perkin reaction, and also by the Knoevenagel or Doebner modification.

RCH=CHCH=CCO2H. 1-Alkyl and 1-aryl derivatives of 4-phenyl-

 \dot{R}' but adicne-1-carbovylic acid are prepared from einnamal deby de and substituted acetic acids in the usual Perkin reaction

RCH=CCH=CH₂. 1-Phenylbutadiene-2-carboxylic acid is obtained

ĊO₂H

by condensation of benzaldehyde with crotonic anhydride in the presence of triethylamine.* The corresponding 3-methyl homolog is obtained by using β -methylcrotonic anhydride **

RCH=CCH=CHR. 1,4-Diarylbutadiene-2-carboxylic acids are ob-

¢o₂H

tained by condensing benzaldehydes with \(\beta\)-benzalpropionic acid.122

111 Thiele, Ann., 306, 154 (1900) Schenck, J. pratt, Chem., [2] 141, 299 (1934).

RCH—CHC—CHCH—CHR. A small amount of 1,6-diphenylhexa-

tricne-3-carboxylic acid is formed by condensing cinnamaldehyde with sodium β -benzalpropionate and acetic anhydride under mild conditions, 123 but this does not appear to be a satisfactory preparative method.

Cyclic Compounds

 γ -Alkyl-and γ -aryl-paraconic acids are obtained by warming aliphatic and aromatic aldehydes with sodium succinate and acetic anhydride at 100–125° (Fittig's synthesis). At higher temperatures, or on heating the paraconic acids,

 β , γ -unsaturated acids and γ -butyrolactones are formed.

Phthalylacetic acid ($R = CO_2H$) is prepared from phthalic anhydride, potassium acetate, and acetic anhydride. With phenylacetic acid and others, at higher temperatures, decarboxylation occurs and benzalphthalide ($R = C_6H_5$, etc.) is formed. Disubstituted compounds can

be obtained from phthalic anhydride and disubstituted acctic acids.

Coumarin and ring-substituted coumarins can be prepared by heating salicylaldehydes with acetic anhydride and sodium acetate. α -Alkyl and α -aryl coumarins are obtained from substituted acetic acids. Certain α,β -disubstituted

coumarins can be prepared from o-hydroxy aryl ketones. 124, 125

RCH=

5-Benzalrhodanine and related compounds can be prepared by reaction of benzaldehyde and its derivatives with rhodanine. 3-Substituted rhodanines may also be used.

5-Benzal derivatives of 4-oxazolone (azlactones) are prepared from benzaldehydes and hippuric acid ($R' = C_6H_5$). Other acyl derivatives of glycine give similar compounds ($R' = CH_3$, $CH_2C_2H_5$, etc.).

¹²³ Knell, Dissertation, Munich (1902); reported by Smedley, J. Chem. Soc., 93, 373 (1908), and by Kuhn and Winterstein, reference 46, p. 220.

¹²⁴ Bargellini, Gazz. chim. ital., 41, I, 737 (1911); Atti accad. Lincei [6] 2, 178, 261 (1925)
C. A., 20, 595 (1926).

125 Flynn and Robertson, J. Chem. Soc., 215 (1936),

5-Benzal derivatives of hydantoin (R' = H). 2-thiohydantoin, creatinine, and a number of similar compounds can be prepared from benzaldehyde and the appropriate derivatives of elycine.

Indirect Syntheses

The products obtained directly in the Perkin reaction and its various ramifications often serve as intermediates for the preparation of other types of compounds. The following paragraphs are intended merely to indicate in a brief way the essential operations involved in typical syntheses that have some preparative value. For convenience the types are listed for anyl compounds (where the starting material would usually be benzaldchyde). In many instances the reactions used are applicable also to compounds with other organic radicals (R = alkyl, vinyl or propenyl, styryl, 2-furyl, etc.)

RCH=CH2. Styrene and \$-alkylstyrenes can be obtained by the thermal decarbovylation of the corresponding cianamic acid. 128 A very general method that can be applied to alkyl and anyl derivatives of acrylic acid consists in adding hydrobromic acid (or hydriodic acid) at low temperature, and treating the resulting β -haloacid with sodium carbonate, 127, 128

RCH=CHBr. β-Bromostyrenes are obtained by heating the dibromide of the corresponding cinnamic acid with sodium carbonate solution,120 or with potassium (or sodium) acetate. 120

β-Alkyl-β-bromostyrenes in can be prepared from the dibromides of α-alkylcinnamic acids by use of alcoholic sodium acetate (75% yields). 1-Bromoolefins can be obtained from alkylacrylic acids, preferably by dehydrohalogenation of the dibromides with pyridine.122

RC=CH. Arylacetylenes and alkylacetylenes may be prepared from the corresponding bromostyrenes or 1-bromoolefins, obtained as de-

- 136 Abbott and Johnson, Org Syntheses Coll Vol., I, 430 (1932).
- 127 Fittig and Binder, Ann . 155, 131 (1879).
- 119 Young, Dillon, and Lucas, J. Am. Chem. Soc., 50, 2533 (1929).
- 118 Nef, Ann., 308, 207 (1899); Straus, Ann., 342, 220 (1905), Manchot, Ann., 387, 282
- 130 Straus, Ber., 42, 287S (1909), see also Adams and Johnson, "Laboratory Experiments (1912). in Organic Chemistry," The Macmillan Co., New York, third edition (1940), p. 309.
- 1st Bogert and Davidson, J. Am. Chem. Soc., 54, 337 (1932). 111 Bachman, J. Am. Chem. Soc., 55, 4279 (1933); Farrell and Bachman, ibid., 57, 1281 (1935).

arylpropiolic ester by hydration with cold sulfuric acid, 145 or by addition of a secondary amine and subsequent hydrolysis of the β-dialkylaminocinnamic ester. 145

o-RCH₂COC₆H₄CO₂H. Acetophenone-o-carboxylic acid (R = H) and ω -substituted derivatives ($R = C_6H_5$, etc.) can be obtained by hydrolysis of phthalylacetic acids or benzalphthalides, produced by interaction of phthalic anhydride and acetic anhydride, phenylacetic acid, etc. (see p. 223).

RCH2CHCO2H. Substituted alanines can be obtained from the cor-

 NH_2

ŃΗ

responding azlactones by reduction (or catalytic hydrogenation) and hydrolysis of the resulting saturated acylamino derivative (see p. 231). The details of the procedure may be varied according to the nature of the groups present, and this series of transformations has been used for a variety of substituted alanines.

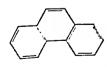
The condensation products from aldehydes and rhodanine may be used in a similar way to obtain substituted alanines.⁵³

RCHCH₂CO₂H. Derivatives of g-alanine may be obtained by the

action of an excess of hydroxylamine on substituted acrylic acids, or their esters. If a large excess of ammonia or methylamine is used in the Knoevenagel modification, β -aryl- β -aminopropionic acids may be formed in considerable amount along with the β -arylacrylic acid. Si

RCH₂CH₂NH₂. γ -Substituted propylamines can be obtained by reduction or catalytic hydrogenation of β -substituted acrylonitriles (RCH=CHCN), obtained from aldehydes and cyanoacetic acid as outlined above.

RCH₂CH₂CO₂H. γ -Substituted butyric acids can be obtained by hydrogenation of the β , γ -unsaturated acids obtained by Fittig's paraconic acid synthesis.



Derivatives of cinnamic acid have been of great value for the synthesis of a number of polycyclic systems. In 1898 Pschorr 122 developed a very general method for the synthesis of phenanthrene and its derivatives, and this has found wide application

10 Perkin, J. Chem. Soc., 45, 174 (1884).

in Moureu and Lazennec, Bull. esc. clim., [3] 35, 1191 (1995).

in Posner, Ber., 25, 4309 (1993); 23, 2320 (1995); Ann., 289, 33 (1912).

in Pechoir and collaborators, Ber., 29, 495 (1895); 23, 162, 176, 1810, 1825, 1829 (1990); 34, 395 (1991); 35, 4499, 4412 (1992); 39, 3105 (1995); Ann., 391, 49 (1912), and other papers. For an expellent survey of Pschorr's synthesis see Fleser, reference 149.

in studies of morphine derivatives, carcinogenic hydrocarbons, etc. 169
The essential features of Pschorr's synthesis are illustrated by the
method used to prepare phenanthrene-9-carboxylic acid. c-Nitrobenzaldehyde was condensed with sodium phenylacetate to give a-phenyl2-nitrocinnamic acid; this was reduced to the corresponding amino acid
(7.7% yield), which was diazotized and treated with copper powder, as
catalyst, to effect ring closure to phenanthrene-9-carboxylic acid (II,
33% yield). The latter gave phenanthrene upon decarboxylation (64%
yield).

A similar series of reactions starting from o-nitrobenzaldehyde and sodium α -naphthylacetate leads to chrysene-5-carbovylic acid (III), ¹⁰⁰ which yields chrysene on decarboxylation. When o-nitrobenzaldehyde

and sodium \$\textit{\textit{name}}\$-naphthylacetate are used as starting materials, the sub-sequent ring cleame takes place at the 1-or 3-position of the naphthaleon ring leading respectively to 3,4-bcaze-1-phenamhrole acid (1Y, 40%) and 1,2-bcaz-1-anthrole acid (V, 60%). The first synthesis of 1,2-5,6 diberaunthracene was accomplished by means of the Pschorr synthesis starting from the acid obtained by a double condensation of 1,4-benzene-diacetic acid with two moles of o-nitrobenzaleddyck. ***

¹⁰ Fieser, "The Chemistry of Natural Products Related to Phenanthrene," second childon, Reinhold Publishing Corporation, New York (1937), pp. 29-31, 96-98, 343.
¹⁰ Wettenbock and Leby, Menath. 43, 557 (1912)

¹⁰ Cook, J. Chem. Soc. 2524 (1931) Eather workers mustook 1,3-benzanthracene for 3,4-benzophenanthrane, see Wettenböck and Laeb, reference 150, and Mayer and Oppenheumer, Ber. 51, 513 (1918).

¹⁴² Weitzenböck and Khnger, Monatsh., 39, 315 (1918)

scribed above, by dehydrohalogenation with solid potassium hydroxide,¹²³ alcoholic alkalies,¹²³ or preferably with sodium amide.¹²⁴ Alkyl derivatives of phenylacetylene may be prepared from the corresponding β-alkyl-β-bromostyrenes,¹²¹ or by alkylation of phenylacetylene with alkyl sulfates or toluenesulfonates.¹²⁵

RCH₂CHO. Arylaectaldehydes may be prepared by addition of hypochlorous acid to cinnamic acid, and heating the α-chloro-β-hydroxy acid with sodium hydroxide or carbonate solution.¹²⁵

A more refined method consists in treating the acrylic amides with hypochlorite in the presence of methanol, and hydrolysis of the resulting vinyl urethane with dilute acid.

RCH=CHCONH₂
$$\xrightarrow{\text{NaOCl}}$$
 RCH=CHNHCO₂CH₂ $\xrightarrow{\text{HoH}}$ RCH=CH=O + NH₂, etc.

This procedure, due to Weerman,¹²⁷ has permitted the synthesis of several difficultly accessible aldehydes.¹²³

RCH₂CH=NOH. Substituted acetaldehydes may also be obtained via the acetaldoximes, which can be prepared in excellent yields from benzalrhodanines, etc. (see p. 230).^{25, 102}

 RCH_2CO_2H . Substituted acetic acids may be obtained by peroxide oxidation of the substituted pyruvic acids, which are secured by way of the azlactone synthesis (see p. 230). They are also obtained in good yields from the substituted acetaldoximes, by dehydration to the nitriles, $RCH_2C\equiv N$, and subsequent hydrolysis (see p. 230).

RCH₂C=N. These may be prepared in good yields by dehydration of the corresponding substituted aldoximes (see preceding paragraph).

RCH₂CH₂NH₂. β-Substituted ethylamines may be obtained by reduction or by eatalytic hydrogenation of RCH₂CH—NOH, RCH₂CN, or RCH—CHNHCO₂CH₃ (see under RCH₂CHO).

RCH₂CH₂CO₂H. β-Substituted propionic acids are prepared readily from the corresponding acrylic acids by reduction with sodium amalgam, by electrolytic reduction,¹²⁹ or by catalytic hydrogenation.

¹²² Hessler, Org. Syntheses Coll. Vol., I, 428 (1932).

¹²⁴ Bourguel, Ann. chim., [10] 3, 225 (1925); Org. Syntheses Coll. Vol., I, 185 (1932).

¹²⁵ Truchet, Ann. chim., [10] 16, 309 (1931); Johnson, Schwartz, and Jacobs, J. Am. Chem. Soc., 60, 1882 (1938).

¹²² Erlenmeyer and Lipp, Ann., 219, 182 (1883); Forrer, Ber., 11, 982 (1878).

¹⁸⁷ Weerman, Ann., 401, 1 (1913); Rec. trar. chim., 29, 18 (1910); 37, 1 (1917).
¹²³ Rinkes, Rec. trar. chim., 39, 200, 704 (1920); 45, 819 (1926); 46, 268 (1927); 48, 960 (1929).

¹²³ Ingersoll, Org. Syntheses Coll. Vol., I, 304 (1932).

RCH₂CHCO₂H. α₁β-Disubstituted propionic acids are obtained by

reduction of the corresponding acrylic acids

duction of the corresponding RCHCH₂CO₂H. β₁β-Disubstituted propionic acids can be prepared

R'
by addition of aromatic hydrocarbons to cinnamic acids in the presence by addition of aromatic nyorocatoous or commented arias in the presence of sulfuric acid, 140 or preferably aluminum chloride 14 Grigard reagents of sulfuric acid, or presented unguard reagents undergo 1,4-addition to α,β-unsaturated esters to give derivatives of

β-disubstituted proposing acres.

RCH—CHCN. β-Substituted acrylonitriles can be prepared by decar-RCH=CHCN. ρ-outstream of the α-cyanoacrylic acids, obtained by condensation of the α-cyanoacrylic acids, obtained by condensation of the α-arrel defined. boxylation of the a-cyanoscapin. The a-aryl derivatives of surface of a cyanoacetic acid with aldehydes. The a-aryl derivatives of surface of the abstained directly by condensation of the abstained directly by condensation of the action of cyanoacetic acid with another the condensation of β arylacry-lonitriles can be obtained directly by condensation of benyl cyanide

th aromatic aldenyoses.

RCm=CCO₂H. Substituted propiolic acids may be obtained by dehy-RC=ECCO2H. Substitutes provides of the corresponding cinnamic

sters. 1st

RCH=CHCO₂C₂H₃
$$\xrightarrow{\text{Der}}$$
 RCHBrCHBrCO₂C₃H₃ $\xrightarrow{\text{Eog}}$ RC=CCO₄H

The free acid is not used as this would favor decay.

The free acid is not used as this would favor decarbory leting to form the The free acid is not used as an accessory product even when the β -bromostyrene, which is formed as an accessory product even when the

RCH_COCO_H. \$\text{Substituted pyruvic acids can be prepared in good} RCH₂COCO₂H. p-substitutes P₂ and secus can be prepared in good yields by hydrolysis of the corresponding adhiopyrm. or excyrlamino yields by hydrolysis of the corresponding adiactors in conceptamino acids 100 (see p. 263). The corresponding adhipyratic acids can be yieus (see p. 253). The condensation product adds can be obtained by hydrolysis of the condensation product formed from tho-

ntine and aromatic aldenyus vac y way, unite and aromatic aldenyus vac y way, and are way, and a RCOCH₂CO₂C₂H₅ Believy and the first and be prepared by addition of bromine to ethyleinnamate, dehydrohalographic under mild condiof bromine to ethyleinnamese, only organism to be adjusted and treatment of the adjusted and tions to a-bromoeinnamic acid, and treatment of the adjusted auditions to a-broad sulfuric acid. 144

The aroylacetic esters can also be obtained from the COTC2-L1s.

Wilderman and A. Chem.
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 Abbott. Org. Syntheses. 12, 60 (1932); no also Pedia.
 Abbott. Org. Syntheses. 13 (1931).
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 Liebermann and Sichse, Ber., 24, 4113 (1891).

arylpropiolic ester by hydration with cold sulfuric acid, 145 or by addition of a secondary amine and subsequent hydrolysis of the β -dialkylaminocinnamic ester. 146

 $o\text{-RCH}_2\text{COC}_6\text{H}_4\text{CO}_2\text{H}$. Acetophenone-o-carboxylic acid (R = H) and ω -substituted derivatives (R = C₆H₅, etc.) can be obtained by hydrolysis of phthalylacetic acids or benzalphthalides, produced by interaction of phthalic anhydride and acetic anhydride, phenylacetic acid, etc. (see p. 223).

RCH₂CHCO₂H. Substituted alanines can be obtained from the cor-

NH₂ responding azlaetones by reduction (or catalytic hydrogenation) and hydrolysis of the resulting saturated acylamino derivative (see p. 231). The details of the procedure may be varied according to the nature of the groups present, and this series of transformations has been used for a variety of substituted alanines.

The condensation products from aldehydes and rhodanine may be used in a similar way to obtain substituted alanines.⁵³

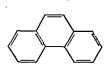
RCHCH₂CO₂H. Derivatives of β-alanine may be obtained by the

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action of an excess of hydroxylamine on substituted acrylic acids, or their esters. If a large excess of ammonia or methylamine is used in the Knoevenagel modification, β -aryl- β -aminopropionic acids may be formed in considerable amount along with the β -arylacrylic acid. ⁸⁴

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RCH₂CH₂CO₂H. γ -Substituted butyrie acids can be obtained by hydrogenation of the β , γ -unsaturated acids obtained by Fittig's paraconic acid synthesis.



Derivatives of cinnamic acid have been of great value for the synthesis of a number of polycyclic systems. In 1898 Pschorr 143 developed a very general method for the synthesis of phenanthrene and its derivatives, and this has found wide application

¹⁴⁵ Perkin, J. Chem. Soc., 45, 174 (1884).

¹⁴⁵ Moureu and Lazennec, Bull. soc. chim., [3] 35, 1191 (1906).

¹⁶⁷ Posner, Ber., 36, 4309 (1903); 38, 2320 (1905); Ann., 389, 33 (1912).

¹⁴³ Pschorr and collaborators, Ber., 29, 496 (1896); 33, 162, 176, 1810, 1826, 1829 (1900);
34, 3998 (1901); 35, 4400, 4412 (1902); 39, 3106 (1906); Ann., 391, 40 (1912), and other papers. For an excellent survey of Pschorr's synthesis see Fieser, reference 149.

in studies of morphine derivatives, carcinogenic hydrocarbons, etc. ¹⁴
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(1, 77% yield), which was diazotized and treated with copper powder, as
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93% yield). The latter gave phenanthrene upon decarboxylation (64%
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A similar scries of reactions starting from o-nitrobenzaldehyde and sodium α-naphthylacetate leads to chrysene-5-carbovylic acid (III), 140 which yields chrysene on decarbovylation When o-nitrobenzaldehyde

and sodium β -naphthylacetate are used as starting materials, the sub-sequent ring closure takes place at the 1-or 3-position of the naphthalena fing leading respectively to 3,4-bcms-1-phenanthroic acid (1Y, 40%) and 1,2-bcmz-1-anthroic acid (Y, 40%). The first synthesis of 1,2-5,6 dibernanthrocene was accomplished by means of the Pschorr synthesis starting from the acid obtained by a double condensation of 1,4-benzene-discretic acid with two moles of o-nitrobensatelehyde. We

¹⁴⁸ Freser, "The Chemistry of Natural Products Related to Phenanthrene," second edition, Reinhold Publishing Corporation, New York (1937), pp. 28-31, 96-98, 343.
¹⁵⁹ Weitsenbück and Lieb, Jönnath, 33, 557 (1922).

¹⁰⁰ Cook, J. Chem. Soc., 2524 (1931). Earber workers mistook 1,2-benzanthracene for 3,4-benzophenanthrane, see Wettsenbick and Lach, reference 150, and Mayer and Oppen hemer, Br. 51, 513 (1915).

ermer, Ber., 51, 513 (1918).

192 Weitzenbock and Khager, Monazak., 39, 315 (1918).

The bimolecular reduction of methyl cinnamate by means of amalgamated aluminum leads to methyl $\beta_i\beta'$ -diphenyladipate (meso and racemic forms).

$$2C_{6}H_{5}-CH=CH-CO_{2}CH_{3}\xrightarrow{Al-H_{5}}C_{6}H_{5}-CH-CH_{2}-CO_{2}CH_{3}$$

$$C_{6}H_{5}-CH-CH_{2}-CO_{2}CH_{3}$$

Although low yields are obtained in this reduction, it has served as a source of β , β' -diphenyladipic acid, which has been used for the synthesis of chrysene derivatives and of chrysene itself. 153

LABORATORY PROCEDURES

Cinnamic Acid

Using Acetic Anhydride and Potassium Acetate.* A mixture of 21 g. (0.2 mole) of freshly distilled benzaldehyde, 30 g. (0.3 mole) of 95% acetic anhydride, and 12 g. (0.12 mole) of freshly fused potassium acetate is refluxed in an oil bath at 170-175° continuously for five hours, using an air-cooled condenser.

The hot reaction mixture is poured into about 1200 cc. of warm water, part of which is used to rinse the reaction flask, and unchanged benzaldchyde is removed by steam distillation. The residual liquid is cooled slightly, 3–4 g. of decolorizing carbon is added, and the mixture is boiled gently for five to ten minutes. The liquid is filtered rapidly through a fluted filter paper; the clear filtrate is heated to boiling, 12–14 cc. of concentrated hydrochloric acid is added carefully, and the hot solution is cooled rapidly with good stirring. After the cinnamic acid has crystallized completely the crystals are filtered with suction, washed with several small portions of water, and dried. The acid obtained in this way melts at 131.5–132° and is pure enough for most purposes. The yield is 16–18 g. (55–60%).

Using Malonic Acid and a Pyridine Base.¹¹⁷ A mixture of 10.6 g. benzaldehyde (0.1 mole), 10.4 g. malonic acid (0.1 mole), and 9.3 g. α -picoline (0.1 mole) is heated for three to four hours in a water bath at 70°. At the end of this period evolution of carbon dioxide has ceased, and the reaction mixture is then treated with 500 cc. of water and 25 cc. of concentrated hydrochloric acid. Unchanged benzaldehyde is removed by steam distillation, and the cinnamic acid is isolated as described in

^{*} The advantage of potassium acetate over sodium acetate is that a shorter period of heating is required to obtain comparable yields.

¹⁵⁷ von Braun and Irmisch, Ber., 64, 2451 (1931); see also Robinson and collaborators, J. Chem. Soc., 607 (1933); 1412, 1414 (1935).

the preceding paragraph. The product melts at 131.5–132.5° and weighs 8-8.5 g. (51-57%). Substituted benzaldehydes usually give higher yields (80-95%) in this reaction.

p-Methoxycinnamic Acid

A solution of 13.6 g. (0.1 mole) of anisaldehyde and 12.6 g. (0.12 mole) of malonic acid in a small quantity of 95% ethyl alcohol is treated with 21 g. of an 8% solution of ammonis (0.1 mole) in 95% ethyl alcohol, and the mixture is heated on a steam bath. After the alcohol has distilled, the oily residue is heated on a vigorously boiling water bath until evolution of earbon dioxide has ceased and the mixture becomes solid (about two hours).

The product is treated with warm water and dissolved by the addition of a minimum amount of sodium carbonate. The solution is boiled a few minutes with 1–2 g. of decolorizing charceal and filtered through a fluted paper. The warm filtrate is poured with stirring into an excess of cold 20% sulfuric acid containing some chopped ice. After the acid has reystallized completely it is collected with suction, washed with several small portions of cold water, and dried. The yield is 8–9 g. (45–50%),* and the product melts at 106–168°.

β-Piperonylacrylic Acid (3,4-Methylenedioxycinnamic Acid)

Forty-five grams of piperonal (0.3 mole), 60 g. of malonic acid (0.576 mole), 120 cc. of dry pyridine, and 3 cc. of piperidine are placed in a 300-cc. round-bottomed flask fixted with a reflux condenser and calcum chloride tube, and heated for one hour on a steam bath. The solution, which at the end of that time is clear, is then boiled gently over a flame which at the end of that time is clear, bethe boiled gently over a flame which at the end of that time is clear, bethe boiled gently over a flame which at the contents of the flask are cooked and poured with string into a nisture of 175 cc. of concentrated hydrochloric acid and 300 g. of chopped ice. The precipitate is filtered with suttion, then washed once with 25 cc. of 10% hydrochloric acid and twice with 25-cc. portions of water. After drying, the acid melts at 227–2309 (uncor.), and weights 40-53 g. (85–90%). The recorded melting point of β-piperonylacrylic acid is 233 (cc.).

A large excess of malonic acid is used to obtain a good conversion of the aldehyde. A ratio of 1.9 moles per mole of aldehyde was found to be near the optimum; with 1.6 moles the yield was 57%, and with 1 mole it fell to 65%. The Dockmer modification is used generally for the less fell to 65%.

Higher yields are reported in the hierature (see Table III, p. 260) but could not be duplicated in the Cornell Indoorstory.

common aldehydes, where a good yield is important, and also for aldehydes that do not give good yields in the usual Perkin reaction.

The presence of water in the reagents causes a marked lowering of the yields. Pyridine should be dried thoroughly over solid caustic and redistilled; higher-boiling pyridine bases (boiling up to 165°) give as good yields as pyridine, when dried thoroughly and distilled. When higher bases are used the reaction mixture is heated for two hours on the steam bath instead of one hour followed by twenty minutes' boiling.

This general procedure is essentially that described in the literature for several alkoxybenzaldehydes.^{154, 155} By the directions given above, 4-methoxy- and 3,4-dimethoxy-benzaldehyde furnish p-anisyl- and veratryl-acrylic acids, respectively, in 80% yields. p-Dimethylaminobenzaldehyde is reported to give the corresponding cinnamic acid in 80% yield by a similar procedure.⁷⁴

3-Methoxy-4-Hydroxycinnamic Acid (Ferulic Acid)

A solution of 15.2 g. (0.1 mole) of vanillin, 23 g. (0.22 mole) of malonic acid, and 1 g. (1.2 cc., 0.012 mole) of piperidine in 50 cc. of dry pyridine is allowed to stand at room temperature for three weeks. During this time the reaction mixture is protected by a soda-lime tube but must not be corked as carbon dioxide is evolved; a Bunsen valve may be used.

The reaction mixture is poured with stirring into a mixture of 60 cc. of concentrated hydrochloric acid and 100 g. of ehopped ice. The acid precipitates at once, and after standing until separation is complete it is filtered with suction. The product is washed with 10 cc. of 5% hydrochloric acid, followed by two 10-cc. portions of water, and then dried. The yield of ferulic acid, m.p. 173° (cor.), is 14-17 g. (70-85%).

This procedure is an adaptation of the Doebner modification developed by Vorsatz ⁸⁶ and is particularly advantageous for preparing cinnamic acids having a free phenolic group. These compounds give low yields at 100° in the Doebner procedure, presumably owing to the ease of decarboxylation of the hydroxycinnamic acids.

The following yields were reported by Vorsatz with other substituted benzaldehydes, with the same proportions of aldehyde and malonic acid: 2,4-dihydroxycinnamic acid (caffeic acid), using 1.4 g. aniline instead of piperidine, allowing to stand overnight, and then warming at 50–55° until evolution of carbon dioxide was essentially complete (about three hours), in 87% yield; 3,4-methylenedioxycinnamic acid (piperonylacrylic acid), using piperidine and standing four weeks at room temperature,

¹⁵⁴ Cain, Simonsen, and Smith, J. Chem. Soc., 53, 1035 (1913).

¹⁵⁵ Haworth, Perkin, and Rankin, J. Chem. Soc., 125, 1693 (1924).

in 83% yield after recrystallization from 75% alcohol; 3.4-dihydroxycommarin-a-carboxylic acid (danhaetin-3-carboxylic acid), using aniline or pyridine and warming for twenty hours at 37°, in 83% yield.

If a large excess of atamonia (60 moles) or methylamine is used in this reaction a mixture of the 8-aminopropionic and acrylic acids is formed.44

a-Methylcinnamic Acid 2

A mixture of 21 g. (0.2 mole) of freshly distilled benzahlehyde, 32 g. (0.25 mole) of propionic anhydride, and 20 g. (0.2 mole) of fused sodium pronionate is heated with occasional shaking for thirty hours in an oil bath at 130-135°. The warm mixture is poured into about 500 ec. of water, stirred thoroughly, and neutralized by the addition of sodium earbonate solution. After removal of unchanced benzaldehyde by steam distillation (or other extraction), the solution is warmed with 3-4 g, of decolorizing carbon and filtered while hot. The warm filtrate is poured slowly, with stirring, into an excess of concentrated hydrochloric acid mixed with channel ice. After the acid has crystallized completely it is collected with section, washed with several portions of water, and dried. The crude product, amounting to 21-25 g., is recrystallized from ligroin and gives 19-23 g. (60-70% yield) of purified material.

The acid obtained in this way may melt at 81° or 74°, as a-methyleinnamic acid exists in two different crystalline forms Both forms have the same configuration (trans Calls CO211) and give the same ester. Occasionally a mixture of the two trans forms is obtained which melts at 77-78°. The true geometrical isomer, allo-a-methyleinnamic acid (cis Colls: COall), melts at 91° and can be obtained by long exposure of the ordinary acid to ultra-violet light.

Very little cinnamic acid is formed in this reaction when sodium acctate is used as catalyst. Although some acetic anhydride is formed by the anhydride-salt exchange, the concentration is low and its rate of reaction at 135° is much less than that of propionic anhydride. At higher temperatures more cinnamie acid is formed (p. 213).

The procedure given is essentially that of Edeleano; 156 α-methylcinnamic acid has also been prepared using propionic anhydride and sodium propionate,2 or acetic anhydride and sodium propionate at 100°,14 and by heating benzal chloride with sodium propionate at 150° (Erdmann 188).

¹⁰⁰ Edcleano, Ber., 20, 017 (1887), see also Rupe and Buesit, Ann., 369, 320 (1909) Frdmann, Ann , 227, 248 (1985).

a-Phenylcinnamic Acid 127

In a 200-cc, round-bottomed flask, 17.4 g. (0.10 mole) of dry potassium phenylacetate, 5 g. of dry potassium carbonate (0.035 mole), 0.5 cc. pyridine, 10.6 g. (0.10 mole) freshly distilled benzaldehyde, and 15.3 g. (0.15 mole) freshly distilled acetic anhydride are mixed thoroughly under nitrogen. An air-cooled reflux condenser is attached, and the flask is carefully inserted in an oil bath at 180°. A vigorous bubbling takes place for a few minutes, after which the reaction proceeds quietly. Heating is continued at 180-190° for two hours. The mixture is allowed to cool, and 300-400 cc. water is added with gentle heating to break up lumps. Potassium hydroxide solution (6 N) is added until the solution is basic (about 30 cc. is required), but care should be taken not to add a large excess of base as the potassium salt of the acid is easily salted out of solution. The mixture is heated until all soluble material has dissolved; some oily material will remain undissolved. The flask is cooled under the water tap and the solution extracted with 300-400 cc. of ether to remove unchanged benzaldehyde and a little stilbene (ca. 1 g.). The water solution is acidified with 6 N hydrochloric acid (15-20 cc. is required), the precipitated acid filtered off, and the filtrate tested with more acid for completeness of precipitation. The precipitate is conveniently dried on a porous plate in a vacuum desiccator. The yield of crude acid, melting about 160°, is 13-15 g. (60-65% of the theoretical). It can be recrystallized by dissolving in 50% ethanol at boiling temperature and adding water until the solution is just cloudy. The solution is cooled very slowly, and long needles form gradually. The purified acid amounts to 11-12 g. (50-55% of theoretical) and melts at 168-170° (uncor.). The acid obtained in this way is the trans form.

β-n-Hexylacrylic Acid (a,β-Nonenoic Acid)

In a large flask 114 g. (1.1 moles) of malonic acid is dissolved in 185 cc. of dry pyridine; the reaction is slightly exothermic. The solution is cooled in icc water, and 114 g. (1 mole) of freshly distilled n-heptaldehyde is added with stirring or good shaking. After a part of the aldehyde has been added the mixture rapidly sets to a mush of crystals, but moderate stirring is possible. The mixture is allowed to stand at room temperature for sixty hours with frequent shaking. During this time the mixture froths owing to evolution of carbon dioxide, and at the end most of the

157 This procedure was furnished through the courtesy of Professor C. R. Hauser and Miss Mildred Patterson, of Duke University. It is a modern version of the Oglialoro modification incorporating results of Bakunin and collaborators, and the use of potassium carbonate and pyridine, as suggested by Kalnin's studies.

malonic acid has been consumed. The reaction mixture finally is warmed on a steam bath for eight to nine hours (until evolution of carbon dioxide has ceased) and then poured into an equal volume of water. The oily layer is separated and shaken thoroughly with 300 cc. of 25% hydrochloric acid to remove pyridine. The product is taken up in benzene, washed with water, dried, and distilled under diminished pressure. After a small fore-run of heptallehyde (3–4 g.), the acid is collected at 130–132°/2 mm.; there is little high-boiling residue. With small quantities the yield is 75-80%, but with larger amounts (1 kg. of heptallehyde) the yield is 90-85%.

Zaur ¹⁰ reported that the seid prepared in this way contains about 5% of the β₁γ-isomer, whereas the Knoevenngel procedure using piperidine gives a lower yield and much more impure material Zaur removed the β₁γ-isomer as the γ-lactone by treating the distilled acid with an equal weight of 85γ-8 unifuria ead and stirring for 6 hours at 80γ-8 unshing with water, and then treating the product with sedium carbonate solution. This converts the β₁γ-unsaturated acid to γ-n-amylbutyrolactone (b p. 110-112γ3 mm.), which is insoluble in carbonate and can be removed by extraction with a solvent. From the alkaline solution the putified aβ-homenole acid is regenerated by actidification and redistilled.

o-Nitrophenylpyruvic Acid †

Atlactone from Aceturic Acid and o-Nitrobenzaldehyde. Six grams (0.94 mole) of o-nitrobenzaldehyde, 5.5 g. (0.047 mole) of aceturic acid, and 2.6 g. (0.032 mole) of lased sodium acetate are mixed thoroughly (by grinding in a mortar) and placed in a 125-cc. Erleameyer flask. To the mixture is added 15 cc. (16.2 g. o. 142 mole) of 90-95% acetic anhydride, and the open flask at then heated on the steam bath for two and one-half hours. The flask is cooled to room temperature and allowed to stand for two hours, during which time crystallization occurs. The solid cake of crystals is broken up and washed with three 20-cc. portions of water. The finely crystalline yellow product is diried for twelve hours in a vacuum desiceator over sodium hydrovide and calcium chloride. The yield is 6 g. of crude product (65%) melting at 110-112°. It may be recrystallized from petroleum ether (6 p. 90-100°) to give bright yellow needles of mp. 113 5-114 8°.

Hydrolysis of the Azlactone. Eight grams (0 0345 mole) of the crude azlactone is refluxed with 200 cc. of 1 N hydrochloric acid for two and one-

[•] This procedure is due to Zasz,** who reported also the following yields with higher aldehydes: n-octaldehyde to α.β-decesses and, 75%, adserdishyde to α.β-dedecense and, 65%, α-undecaldehyde to α.β-dedecense and, 65%.

These directions were furnished by Mr Richard B. Hashrourl, Cornell University.

half hours in a reflux apparatus fitted with ground-glass joints. To the hot (90°) solution is added 1–2 g. of charcoal, and the whole is boiled for a few minutes. The boiling solution is then filtered and cooled to room temperature. Most of the o-nitrophenylpyruvic acid separates as an oil, but seeding or scratching causes crystallization to begin. After standing at room temperature for two hours, the mixture is cooled at 0° overnight. The light tan crystals of o-nitrophenylpyruvic acid are filtered, washed with 5 cc. of cold water, and dried in a vacuum desiccator. The product weighs 4.3 g. and melts at 117–120°. The aqueous mother liquor is concentrated in vacuum to about 50 cc., and the oily product is seeded and worked up as before. The second crop of crystals weighs 1.7 g. and melts at 119–120°. The total yield of product is 6.0 g. or \$3% of the theoretical. This product is sufficiently pure for synthetic purposes: it may be recrystallized from water with small loss.

TABLE II

YELDS OF CHMAMIC ACID UNDER VARIOUS CONDITIONS

		Conditions	etto		
Carbonyl Component	Acid Components w moles per mole aldehyde	Temperature,	Time,	Yield,	Reference
Benzaldchyde	Λο ₂ O (1 5 m) + NaOAc (0 65 m) —earne, + trace C ₃ H ₂ N	8 8	op or	48, 52	29, 27
	$Av_2O(2.1 m) + KOAe(0.7 m)$ $Av_2O(1.5 m) + KOAe(0.65 m)$	81 8	× ×	3 2 2	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
	Malonic (12 m) + Act Us (9 65 m) Malonic (12 m) + NIIs (2 m) Malonic and + Ciri N · Ciri	88 89	w m	80-85	8.8
Benzalaniline Benzal chloride	Malonio aced (1 m) NaOhe (4-5 m) or KOAe	20-100	រូន	88	88
Denzal diacetate	110Ac (4 m) + NaOAe (4 m)	160-180	10	2000	នន

TABLE III RING-SUBSTITUTED CINNAMIC ACIDS

	RING-SUBSPITUTED CINNAMIC MULDS	rured CIN	VAMIC AC	IDS		
Substituted		Conditions	tions			
Senzaldehyde (or Other Carbonyl Component)	Acid Components	Tempera- ture, °C.	Time, hours	Substituted Ginnamio Acid (or Other Product)*	Yield,	Reference†
, tr	Medicals (1.9 m) ± NH, (9.5 m)	100 180	-+	3-Phioro-	50	158
2-Chlore	Acco (2.1 m) + NaOAe (0.7 m)	180-200	s	2-Chloro-	66, 71	29, 27
	$Ae_2O(2.1 m) + IXOAe(0.7 m)$	180-200	s		22	50
(2-Chlorobenzal	110Ac (1.8 m) + KOAc (5 m)	210	40	2-Chloro-	Good	159
3-Chlore-	$\Lambda e_{2}O(2.1 m) + NaOAe(0.7 m)$	180	s	3-Chloro-	83	27
-Chloro-	Ac20 (2.1 m) + NaOAc (0.7 m)	180	တ	-i-Chloro-	52	27
2-Chloro-6-fluoro-	Malonic (1.5 m) + IIOAc	100	9	2-Chloro-6-fluoro-	8	160
2,5-Dichloro-	$Ac_2O(2.1 m) + NaOAc(0.7 m)$	180	ø	2,5-Dichloro-	28	27
2,6-Dichloro-	$\Lambda c_2 O(2.1 m) + N n O \Lambda c(0.7 m)$	180	တ	2,6-Dichloro-	83	27, 161
3,5-Dichloro-	$Ac_2O(0.8 m) + NaOAc(1.3 m)$	061	18	2,5-Dichloro-	20	162
3,5-Dichloro-2-nitro-	$\Lambda c_2 O(1.5 m) + NaOAc(1 m)$	180	2	3,5-Dichloro-2-nitro-	65	163
2,3,4-Trichloro-	Ac20 + NaOAc	(081)	(S)	2,3,4-Trichloro-	Good	1 91
2,3,6-Triebloro-	$Ac_2O(2.1 m) + NaOAe(0.7 m)$	180	တ	2,3,6-Trichloro-	99	27
2,4,5-Trichloro-	Ac2O + NaOAc	(081)	8	2,4,5-Trichloro-	Good	164
Pentachloro-	$Ae_2O(3.5 m) + NaOAe (1 m)$	170-180	99	Pentachloro-	30	179
2-Bromo- 2-Bromobenzal	Malonic (1.8 m) + IIOAc (1.5 m)	100, 190	9	2-Bromo-	Good	160
diacetate	Ac20 + NnOAc	165-190	0		Good	165
3-Bromo-	Malonic acid + Collon + Collin	115	7	3-Bromo-	83	63
3,4,5-Tribromo-	$Ac_2O(25 m) + NnOAc(4 m)$	Rcfl.	-	3,4,5-Tribromo-	53	180

5	3	21	168	167	5 5	77	168	8	5	100	9 6	73	8	3	2	27	8	8	3	171	172	1	: !	171	1	121		7	174	27	27	27	101
95	8 6	8	8	67	1	2 ;	98	73	S	76	2 6	0	23	£	8	83	96	8	3 1	8		ā	\$	₽		23	۶		2000	-	12	23	_
Tabama-2-nitra-	0 T-1-	- comp	-opog-	Z-Nitro-						3-Nitro-			_		-califfo-				2. Notront oblane	-Omino-seguing-	2-Nuro-5-chloro-	3-Nitro-4-chloro-	2-Natro-4-brome	O Marie & Process	- Mino-o-promo-	-Nitro-5-bromo-	2,4-Dinitro-	2.6-Danitro-	Mone	anoni .	Z-Methyl-	4-Methyl-	3-Methyl-6-nitro-
9	¥	;	0	0.75	00	=	2	Ť,	~	13	œ	7		4 0	•	*0		64	0		0	-	5		. ;		BO	00	Varied		0 0	•	
Refi	350	P-0		3	180	190	1	9	2	8	981	-	٤	3 5	3	2 8	2 ;	3	Ref	148	2 0	200	Ken	145	d-d	1	3	145	Vaned	180	8	1	3
Ac20 (25 m) + NaOAc (4 m)	Ac20 (9 m) + NaOAc(1.5 m)	Aco (1.3 m) + NaOAc (1165 m)	Ac.0.2 m + TO101 -1	W TOUGHT IN THE WAY	Acco(21 m) + NaOAc (07 m)	{ Acc0 (2.1 m) + NaOAe (1 m)	Malonic and + C.H.N . Car at	Malonia (19-)	A 20 M - 1 M - 20 M	Ac20 (4 m) + NaUAe (1.5 m)	Ac20 (2.1 m) + NaOAc (0.7 m)	Malonic and + Callan + Callan	Malonio (13 m) + NH, (2 m)	AczO (2 m) + NaOAc (0 8 m)	Acro (2 1 m) + NaOAr (0 7 m)	Malonic acut + C. F. N. + C. M.	Malonie (1.3 and 4 N.H. Cl. and	The state of the s	Acto (7 5 g) + NaOAc (8 g)	AcsO (14g) + NsOAc (66g)	App. (750) + No.03.01 a)	App. 07. N. O. V.	(STIPPOPPE A CONTROL	Acto (1.0 g.) + NaOAc (0.7 g.)	Ac20 (8 g) + NaOAc (1 g)	Acro (21 m) + Nana (07 m)	And large of No. O. A.	(m T) avour + (max) or ar	Acro (2.1 m) + NaOAc (0.7 m)	Acro (2 1 m) + NaOAe (0.7 m)	Acro (2 1 m) + NaOAc (0.7 m)	Malonic and + CallaN + Cat.,N	
Tribromo-2-nitro-	Z-10do-	3-Iodo	2-Nitro-					2-Nitrobenzalanilaa	3-Nitro					4-Nitro				2.Normalaham	2000	- Nitro-Pehioro-	3-Nitro-4-chloro-	2-Nitro-4-brome-	2. Nitro-fahrome	- Oracle Control	- Niro-4-liromo-	2,4-Dinitro-	2,6-Dinitro-	2.4 6-Transme	2.11-11-1	- Stelling	5-Methyt.	3-Methy (-6-nitro-	1

 A name in staines is synonymous to that immediately preceding † Reference 105-232 appear on pp. 264-265.

TABLE HE—Continued Bing-Sunstweited Cinnamic Actus

	CING-SUBSTRUTED CINAMIC VOIDS	ED CINNAM	in vicini			
		Condicions	ions		•	
Sunstituted Benzaldehydo (or Other Carbonyl Component)	Acid Components	Tempera- ture, °C.	Time, hours	Substituted Cinnamie Acid (or Other Product) *	7 ield,	Reference†
4-Methyl-	Ac ₂ O (2.1 m) + NuOAe (0.7 m)	180	x 6	-i-Mothyl-	23, 15 70	27, 28 175
	Malonie acid - CallaN - CallaN	115	Ţ.		87, 70	63, 74
	Mahmie $(1 m) + C_6 H_5 N (0.15 m)$	00 ss	÷ -		(% f).6 (% 1.6	117
4-Methyl-2-chloro-	Malonic neid + Collan	001	~ §	-t-Mothyt-2-chloro-	(50) 7.	182
4-Muthyl-3-nitro-	Ae ₂ O (2 g.) + NnOAo (1 g.) Ae ₂ O (2.1 m) + NnOAu (0.7 m)	180-200	<u> </u>	4-Bthyl-	Truce	SS .
	Malonic neid + CallaN + CallaN	115	<u>.</u>		88	38
2,4-Dimethyl-	Malouie (1 g.) $+ C_6 \Pi_6 N \Pi_3$ Malouie (1,2 m) $+ N \Pi_3$	<u> </u>	က	2,4-Dimethyt-	::	821
2,5-Dimethyl-	Malonic (I g.) + CallaNII2	001	*	2,5-Dimethyl-	:	177
2,6-Dimethyl-	Λe ₂ O (2.1 m) + NαOΛe (0.7 m)	081	S-50	2,6-Dimethyl-	c ;	25
3,1-Dimethyl-	Malonie (1.2 m) + ColloNII2	20-100	 - - - -	3,4-Dimethyl-	Good	178
2,3,4-Trimethyl-	Mulonie (1 m) + CalluN (cree)	001	23	2,3,4-Trimethyl-	<u>e</u>	- 183 - 183
2,4,5-Trimethyl-3,0- dini(ro-	Λc ₂ O (2.3 g.) + ΝαΟΛο (0.7 g.)	<u>\$</u>	S	2,4,5-Trimothyl-3,6- dinitro-	e e	181
2,4,0-Trimethyl-	Ac ₂ O (2.1 m) + NaOAe (0.7 m) Malonic neid + CellaN + CellaN	180	8 [2,4,6-Trimothyl-	2 01	22 23
2,4,18-Trimethyf. 3.5-dinitro	Ae2O (2.1 m) - NaOAc (0.7 m)	180-200	ော	2,4,6-Trimethyl-3,5- dinitro-	8	28

4-Jeopropyl	Act 0 (2.1 m) + Na OAc (0.9 m)	175	9	4-Isopropyl-	42	2
	Malonic (1.2 m) + Cill,N + Cillan	90	8		35	185
2-Incpropyl-5-methyl-	2. Inpenpyl-5-methyl- Malonic and + Chin + Chin	100, 115	2, 1	2-Isopropyl-4-methyl-	99	186
4-Plieny l.	Ar20 (8 m) + NaOAc (1.2 m)	Ref.	œ	4-Phenyl-	:	88
	Ac20 (2 1 m) + NaOAc (0 7 m)	180-200	00		Trace	28
	Malonic (1 1 m) + CH2CO2H	100	22		:	38
2-11ydroxy-	Ac20 (1.6 g) + NaOAc (1.3 g)	Ref.	7,	2-Acetoxy-(and coumarin)		1.34
	Malonic acrd + CallaN + CallaN	115	*	(o-Coumarie acid)	8	2
	Malonic (1 m) + C,H,N (0 15 m)	100, 65	4,4	(Coumarin-e-carboxyle acid)	S	87. 87a
2-Methory-	AryO (2 g.) + NaOAe (0.7 g.)	Ref.	ø	2-Methoxy-	22	30.2
	Ac20 (21 m) + NaOAc (0.7 m)	180-200	00		#	28
	Malonic (1.2 m) + Callan + Callan	5	ĭ		8	185
	Malante (1 m) + CallaN (9 15 m)	8	1.		8	377
2-Methory nitro-	Ar20 (21g) + NaOAc (15g.)	175	60	2-Methoxy-3-nitro-		187
2-Methoxy-5-miro-	Ar20 (3 g.) + NaOAc (1 g.)	Ref.	9	2-Methoxy-5-ntro-	25	188
2-Diboxy.	Acro + NaOAc	165		2-Ethoxy-	:	180
2-13thury-5-nitro-	AcrO (3 g.) + NaOAc (1 g.)	Ref.	9	2-Ethoxy-5-nitro-	:	201
3-ffydroxy-	(Act (25g.) + NaOAc (2g.)	Reft	'n	3-Acetoxy-	è	20 101
	Majorice (1 m) + Quinoline (1 m)	8	9	3-Hydroxy-	٤	
	Matonic (1 m) + Callan (0 15 m)	911	œ		6	87.
	Malonic acid + CallaN + CallaN	901	63		2 8	
3-Methory-	Acro (21 m) + NaOAc (0.7 m)	180-200	œ	3-Methoxy.	\$	98 101
	Malonie and + NIIs	120				30
	Malonic (1 m) + Call N (0 15 m)	8	9-4		8	87, 18
	Malouse (1 2 m) + CallaN + CallaN	100, 115	6,		90.70	103 108
2 Methody - Children	Malonie (2 m) + CallaN + CallaN	100, 115	63	3-Methoxy-2-nitro-	8	194
The factors of a state	- albe	100, 115	e a	3-Methoxy-4-nitro-	95	161
o-Marinity-o-num-	Native	100, 115	64	3-Methoxy-6-nitro-	8	191

A name to italies is syncorrous to that immediately preveding.
 Heterores 150-234 appear on pp. 204-204.

ТАВГВ 111—Сонйниев Выс-Винетегия Опимано Аспря

1	IIING DUMINI COMMINI) Silvers				
		Conditions	HIOLIN	•	;	
Acid Components		Tempera- lare, °G.	Time, hours	Substituted Cinnamic Acid (or Other Product)*	, xield, %	Referonco
Ar2O (1 g.) + NaOAa (1 g.)	[E.)	Ned.	70 E	3-Ethoxy-	:	901
ArgO (3 m) + NaOAs (2.3 m)		9.1	<u> </u>	of acetate)	60, 50	30, 196
4-11ydroxy-3,5-dllodo- Ac2O (8 m) + NnOAc (3.5 m)	(11)	135	<u>:</u>	4-Hydroxy-3,5-diiodo-	8	500
Ae ₂ O (2.2 m) + NaOAe (1 m)	1 111)	Rell.	s	d-Methoxy-	8	S 8
Ac20 (2.1 m) + NaOAc (0.7 m)	.7 m)	180-200	oc -		Q :	8 5
Ac2O (1.5 m) + KOAc (0.6 m)	(111)	<u>S</u>			95 5	07.1
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Λε ₂ Ο (2.5 m) + ΝαΟΛε (1.3 m)	3 m)	1:45	တ	4-Mothoxy-3-nitro-	÷5	201
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Malonio (2.5 m) + CallaN + CallaN	+ CollinN	100	C1	-t-1 [ydroxy-2,5-dimethyl-	:	202
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2,3-Dimethoxy-	Acto (2.1 m) + NaOAc (0.7 m)	180-200	80	2,3-Dimethoxv-	15	86
	ActO (6.5 m) + NaOAc (1.7 m)	200	77		2	204
	Malonic (2 m) + Calin + Calin	100, 115	7		92	202
2.3-Methylenedioxy-	Malonic (2.5 m) + C,H,N + C,H,N	100	1	2.3-Methylenedioxy.	Good	200
2-Ethoxy-3-methoxy-	Malonic (2 m) + Colfin + Collin	100, 115	1,	2-Ethoxy-3-methoxy-	25	202
2,3 Diethoxy	nie (2 m)	100, f15	42	Z,3-Diethoxy.	8	302
2,4-Dinydroxy.	Acco + NaOAc	120	80	(7-Acetoxycoumaria,	30	875 208
	Matonic (1 m) + CaliaN (9.15 m)	282	_	7-bydroxyconmann, or	43	878
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	Malonia and the U.M.	_	_	Z,6-Dimethoxy.	0	
3.4-D.hvdroxv.	Acc (3 e) + No 0 e o				33	212
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	Malonie (2 m) + C.H.N. + C.H.NH.	3 5	= •	e, Lubydroxy	22	8
	Malonie (1 m) + C.H.N (0 15 m)	3 5	,	or collete acid	84	8
	Malonie (2 m) + C.H.N + C.H.N	200	-		7	873
3-Hydroxy-4	willing + while + (m) a more	27-01	weeks		8	873
methoxy-	Malonic (1.5 m) + C,III,N +	100	ಣೆ	3-Hydroxy-4-methows or	8	
	Callin	115	rin	herperette acid, or troferuite	8	172
3-Methoxy-4.				acid		
hydroxy-	Ac20 (3 g.) + NaOAc (1 g.)	Refl	8	2 Methons		
	Malone (1.5 m) + NH1 (1.2 m)	100	~179	3-Methoxy-4-hydroxy- or	:	213
	Malone (3 m) + C.H.N. + C.B.	9	7	feruise acid	8	30
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13,4-Methylonedioxy-	Ac ₂ O (1.8 m) + NaOAα (1 m)	Reff.	2-0	3,1-Mothylenedioxy-	- 1	217
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	Malonia (1 m) + CallaN (0.15 m)	20-100			8	87,
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methoxy-	Malonic (1.5 m) + C_bH_bN + EiOH Malonic (1.2 m) + C_bH_bN + EiOH	9 5		3-Hydroxy-5-methoxy-	:	224	
3,4-Trihydroxy-	Malonic (2 m) + Calin + Calint	i is	ន	C.S. Dahydroxyeoumarin-	: 8	S &	
				3-carboxylic acid or Daph- netin-3-carbozylic acid)			
4.3-Dhydroxy-	Acto + NaOAc	180		(7-Methoxy-8-hydroxy-	:	225	
-6-0-1	Malonie (3 m) + C,III,NH, + EtOH	8		coumarn)	8	300	
2,3,4-Trimethoxy	Melonic (12 m) + CiffN + CiguN	100, 115		2,3,4-Trimethoxy-	8 8	185	
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4-by droxy-		2	21.01	3,5-Dimethoxy-f-bydroxy-	8	230	
3,4,5-Trimethoxy-	A20 (7 m) + NaOAc (3 m)	145	47	3,4,5-Trimethoxy.	2	531	
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4.Acctamida	Malonic and + C.H. C. + C. H. C.	3	œ	(6-Nitrocarbostyryl)	:	232	
4-Acetamado-Intro-	Aco (3 m) + Na OAc (1 5 m)	8	,	4-Acetamodo-	738	7.4	
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CHAPTER 9

THE ACETOACETIC ESTER CONDENSATION AND CERTAIN RELATED REACTIONS

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MECHANISM

The acetoacetic ester condensation * consists in the reaction, in the presence of certain bases, of an ester having hydrogen on the a-carbon atom with a second molecule of the same ester or with another ester (which may or may not have hydrogen on the a-carbon atom) to form a \$B\$-ketoseter. The bases capable of effecting such reactions include sodium alkovides, triphenylmethylsodium, sodium amide, and certain Grignard reagents such as mesitylmagnesium bromide and isopropyl-magnesium hromide; also, metallie sodium effects certain condensations, the sodium alkovide which is formed in the reaction mixture probably serving as the active condensing sgent. The classical example of the acetoacetic ester reaction is the formation of acetoacetic ester itself by condensation of ethyl acetate by means of sodium ethoxide, for which the following reaction may be written.

$$CH_2CO_2C_2H_4 + CH_2CO_2C_2H_4 + NaOC_2H_5 \rightarrow$$

 $CH_2C(ON_2) = CHCO_2C_2H_3 + 2C_2H_4OH_2CHCO_2C_2H_3 + 2C_2H_2OH_2CHCO_2C_2H_3 + 2C_2H_2OH_2CHCO_2C_2H_3 + 2C_2H_2OH_2C_2H_3 + 2C_2H_2C_2H_3 + 2C_2H_3 + 2C_2$

The reaction probably involves an ionic mechanism, a 4 the first step of which is an acid-hase exchange; in the presence of the ethoxide ion the hydrogen on the α -carbon atom is ionized as a proton to form the ester anion (enolate anion), which is probably a resonance hybrid of the two structures "CH—C—0(CML) and CH $_{m}$ —0—0"(OC-ML).

(1)
$$CH_1CO_2C_2H_4 + {}^{\sim}OC_2H_6 \rightleftharpoons (CH_2CO_2C_2H_4)^- + C_2H_4OH$$

The second step involves the condensation of the ester anion with the carbonyl group of a molecule of unchanged ester, presumably forming an intermediate anion (with the charge on the oxygen) which, on release of the ethoxide ion, forms are teacetic ester.

(2)
$$CH_4C$$

$$0$$

$$CH_4CO_4C_4H_4)^- \rightleftharpoons CH_4CO_4C_4H_4 + -OC_4H_4$$

$$CH_4CO_4C_4H_4 \rightleftharpoons CH_4CO_4C_4C_4C_4C_4H_4 + -OC_4H_4$$

* This type of condensation is frequently called a Claimin mection—a term that is used also for certain other types of condensation effected by bees, tricking, is those-set; condensations to form 13-distortions and such abid rescensing as the condensations of other actuals with bensidelyed to form ethyl consequents and of acceptance with bensidebyth to form bensidelyed to form ethyl consequents and of acceptances with bensidetly the form bensidelyed to form the consequence of the condensation of the consequence of the consequence of the condensation of the consequence of the condensation of th

Snell and McElvain, J. Am. Chem. Soc., 53, 2310 (1931).
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¹ Hauser, J., Am. Chem. Soc., 60, 1957 (1938), Aradt and Eastert, Ber., 69, 2384 (1936)

Acetoacetic ester is then converted into its anion by the action of the ethoxide ion; this third step involves an acid-base reaction in which a hydrogen on the α -carbon atom of the β -ketoester is ionized.

(3)
$$CH_1COCH_2CO_2C_2H_5 + -OC_2H_5 \Rightarrow (CH_1COCHCO_2C_2H_3) - + C_2H_3OH$$

Evidence that esters form anions according to the first step of the mechanism is furnished by the racemization of esters of optically active disubstituted acetic acids in the presence of ethoxide ion, and by the hydrogen-deuterium exchange of ethyl acetate and other esters with a-hydrogen atoms in the presence of this base and deutero alcohol. That ester anions are the active intermediates in the condensation is shown by the fact that they may be prepared by means of the stronger base, triphenylmethyl ion, and condensed with esters or other reagents. 5.7.8.9

With ethoxide ion and most esters the equilibrium of the first step is on the side of unchanged ester, and in order for this base to effect the condensation the \beta-ketoester formed must be converted largely into its anion, that is, the third step must take place. With triphenylmethyl ion, however, the equilibrium of the first step is on the side of the ester anion, and the third step is not required for the condensation, although this acid-base reaction does take place when the B-ketoester has an enolizable hydrogen. Thus, in the presence of the triphenylmethyl ion, ethyl isobutyrate may be condensed with ethyl benzoate to form ethyl benzovldimethylacetate 12 even though this β-ketoester is incapable of forming an enolate anion. Ethyl isobutyrate also undergoes self-condensation in the presence of the triphenylmethyl ion (but not in the presence of ethoxide ion) to form ethyl isobutyrylisobutyrate," which is converted into its anion by the ethyl isobutyrate anion or the triphenylmethyl ion; the hydrogen on the γ -carbon atom of the β -ketoester is involved in this third step." These reactions may be represented as follows.

 $C_{\varepsilon}H_{s}COC(CH_{z})_{2}CO_{2}C_{2}H_{s} + -OC_{2}H_{s}$

Kenyon and Young. J. Chem. Soc., 216 (1940).

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 $HC(CH_A,CO_*C_*H_* + [C(CH_A,CO_*C_*H_*]^- \rightleftharpoons$

HC(CH_1)_COC(CH_1)_CO_C_H_6 + -OC_H_6

 $HC(CH_1)_*COC(CH_1)_*CO_*C_*H_4 + [C(CH_1)_*CO_*C_*H_4]^- \rightleftharpoons$ or (Calla)aC-

[C(CH₃)₂COC(CH₃)₂CO₂C₂H₄] - + HC(CH₃)₂CO₂C₂H₄ or (C₄H₄)₃CH

The reversibility of the acetoacetic ester condensation is well established. Certain β-ketoesters, especially those having one or two substituents on the a-carbon atom, are cleaved by alcoholic sodium ethoxide to form esters. Thus, although ethyl a-propionyforopionate is formed by the self-condensation of ethyl propionate in the presence of sodium ethoxide, when treated with alcoholic sodium ethoxide it reverts to ethyl propionate; 12 similarly, ethyl diethyfacetoacctate is cleaved by alcoholic sodium ethoxide to form ethyl diethylacetate and ethyl ncetate 12

 $CH_1CH_2COCH(CH_1)CO_2C_2H_6 \xrightarrow{N_4OC_2H_6} 2CH_1CH_2CO_2C_2H_6$

 $CH_1COC(C_2H_4)_1CO_2C_2H_4$ $\xrightarrow{N_4OC_2H_4}$ $\xrightarrow{C_1R_1OH}$ $HC(C_2H_5)_2CO_1C_2H_5 + CH_1CO_2C_2H_5$

An interesting example is the reversion of the product from ethyl isobutyrate and ethyl benzoate. Although ethyl benzoyldimethylacetate is obtained by short treatment of these esters with triphenylmethylsodium, " on standing in the presence of sodium ethoxide and triphenylmetbane (both of which are by-products of the condensation) it reverts to ethyl benzoate and ethyl isobutyrate, the latter undergoing selfcondensation to form ethyl isobutyrylisobutyrate which is converted into its sodium derivative.13 These reactions can be followed from the ionic equations represented above.

There seems little doubt that the acctoacctic ester condensation is influenced in the first step by the acidic strength of the ester 4 and by the basic strength of the condensing agent," in the second step by the rate and position of equilibrium of the reaction of the ester anion with ester,14 and in the third step by the acidic strength of the β -ketoester and the strength of the base. At least with triphenylmethy sodium the first and third steps are relatively rapid and complete and the second step is relatively slow. Apparently, the influence of structure on the overall reaction is most pronounced in the second step. 4 In general, it may be

¹¹ Dieckmann, Ber., 33, 2670 (1900).

¹¹ Hudson and Hauser, J. Am. Chem. Soc., \$2, 62 (1910). 14 Abramovitch and Hauser, unpublished observations.

stated that the acetoacetic ester type of condensation will take place when a base is formed which is weaker than that used as the condensing agent. Thus, in the formation of ethyl acetoacetate from ethyl acetate and sodium ethoxide, the enolate anion, (CH₃COCHCO₂C₂H₅)⁻, is weaker than the ethoxide ion, and in the formation of ethyl benzoyldimethylacetate from ethyl isobutyrate and ethyl benzoate in the presence of triphenylmethylsodium the ethoxide ion (a by-product of the condensation) is weaker than the triphenylmethyl ion.

SCOPE AND LIMITATIONS

The acetoacetic ester type of reaction is used to prepare a variety of β -ketoesters and certain other types of compounds. The self-condensation of esters having hydrogen on the α -carbon atom may be effected readily; this amounts to an acylation of the ester by another molecule of the same ester.

$$\begin{split} & \text{RCH}_2\text{CO}_2\text{C}_2\text{H}_5 + \text{H---CHRCO}_2\text{C}_2\text{H}_5 \rightarrow \text{RCH}_2\text{COCHRCO}_2\text{C}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OH} \\ & \text{R}_2\text{CHCO}_2\text{C}_2\text{H}_5 + \text{H----CR}_2\text{CO}_2\text{C}_2\text{H}_5 \rightarrow \text{R}_2\text{CHCOCR}_2\text{CO}_2\text{C}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OH} \end{split}$$

The condensation between two different ethyl esters may be indicated as follows.

$$RCO_2C_2H_5 + H - C - CO_2C_2H_5 \rightarrow RCOCCO_2C_2H_5 + C_2H_5OH$$

The first ester may be designated as the acylating ester. This condensation is generally satisfactory only when one of the esters (the acylating ester) has no active hydrogen. The condensation of two esters each of which has active hydrogen atoms may result in the formation of a mixture of four different β -ketoesters, the two self-condensation products and the two mixed ester condensation products, although in certain cases one of the latter may be the principal product. Even the application of the special technique of first converting one of the esters largely into its sodium enolate by means of triphenylmethylsodium and then condensing the enolate with an ethyl ester has not been particularly successful thus far, as mixtures of β -ketoesters are still obtained. Certain acylations by means of phenyl or diphenyl esters, however, have been successful.

Three of the more common esters which have no active hydrogen and which have served satisfactorily as acylating esters are ethyl formate,

¹³ Hudson and Hauser, J. Am. Chem. Soc., 63, 3156 (1941).

ethyl benzoate, and ethyl exalate. General reactions with these esters are indicated in the following formulations.

$$\begin{split} & \text{HCO}_1 C_1 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_1 C_2 H_5 \rightarrow \text{HCO} - \overset{\frown}{C} - \text{CO}_1 C_1 H_4 + C_2 H_4 \text{OH} \\ & \text{C}_4 H_4 \text{CO}_4 C_1 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_1 C_2 H_5 \rightarrow \text{C}_4 H_4 \text{CO} - \overset{\frown}{C} - \text{CO}_4 C_2 H_5 + C_1 H_4 \text{OH} \\ & \text{CO}_5 C_1 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_4 C_2 H_5 \rightarrow \overset{\frown}{C} - \text{CO}_5 C_2 H_5 \\ & \text{CO}_4 C_1 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_4 C_3 H_5 & \text{CO}_4 - \overset{\frown}{C} - \text{CO}_2 C_3 H_6 \\ & \text{CO}_5 C_1 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_4 C_3 H_5 & \text{CO}_4 - \overset{\frown}{C} - \text{CO}_2 C_3 H_6 \\ & \text{CO}_5 C_3 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_4 C_3 H_6 & \text{CO}_4 - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 \\ & \text{CO}_5 C_3 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 & \text{CO}_4 - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 \\ & \text{CO}_5 C_3 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 & \text{CO}_4 - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 \\ & \text{CO}_5 C_3 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 & \text{CO}_4 - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 \\ & \text{CO}_5 C_3 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 & \text{CO}_4 - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 \\ & \text{CO}_5 C_3 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 & \text{CO}_4 - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 \\ & \text{CO}_5 C_3 H_4 + \text{H} - \overset{\frown}{C} - \text{CO}_5 C_5 H_6 & \text{CO}_5 - \overset{\frown}{C} - \text{CO}_5 C_3 H_6 \\ & \text{CO}_5 C_3 H_6 + \text{H} - \overset{\frown}{C} - \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H_6 \\ & \text{CO}_5 C_5 H$$

The ethoxalyl derivatives may lose carbon monoride to form malonic ester derivatives when heated; the reaction serves as a good method for the preparation of certain of these compounds.¹⁵

Similarly, ethyl formate and ethyl oxalate acylate ethyl crotonate and ethyl sorbate, the vinylogs of ethyl acetate.

$$\text{HCO}_2\text{C}_2\text{H}_1 + \text{CH}_4(\text{CH} = \text{CH})_*\text{CO}_2\text{C}_2\text{H}_4 \rightarrow \\ = 1 \text{ or } 2$$
 $\text{HCOCH}_2(\text{CH} = \text{CH})_*\text{CO}_2\text{C}_2\text{H}_4 + \text{C}_2\text{H}_4\text{OH}_$

$$\begin{array}{c} \operatorname{CO}_1C_2\Pi_1 + \operatorname{CH}_1(\operatorname{CH} = \operatorname{CH})_*\operatorname{CO}_1C_1\Pi_1 \\ | & = 1 \text{ or } 2 \end{array} \rightarrow \\ \operatorname{CO}_1C_1\Pi_1 \qquad \qquad \\ \operatorname{COCH}_1(\operatorname{CH} = \operatorname{CH})_*\operatorname{CO}_1C_1\Pi_1 + \operatorname{C}_1\Pi_1\operatorname{OH} \\ | & = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{CH})_*\operatorname{CO}_1C_1\Pi_1 + \operatorname{C}_1\Pi_1\operatorname{OH} \\ | & = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{CH})_*\operatorname{CO}_1C_1\Pi_1 + \operatorname{C}_1\Pi_1\operatorname{OH} \\ | & = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{CH})_*\operatorname{CO}_1C_1\Pi_1 + \operatorname{C}_1\Pi_1\operatorname{OH} \\ | & = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{CH})_*\operatorname{CO}_1C_1\Pi_1 + \operatorname{C}_1\Pi_1\operatorname{OH} \\ | & = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{CH})_*\operatorname{CO}_1C_1\Pi_1 + \operatorname{C}_1\Pi_1\operatorname{OH} \\ | & = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{CH})_*\operatorname{CO}_1C_1\Pi_1 + \operatorname{C}_1\Pi_1\operatorname{OH} \\ | & = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{CH})_*\operatorname{CO}_1C_1\Pi_1 + \operatorname{C}_1\Pi_1\operatorname{COCH} \\ | & = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{CH})_*\operatorname{COCH} \\ | & = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} = \operatorname{COCH}_1(\operatorname{CH} =$$

¹⁴ See, for example, Cox and McElvain, Org. Syntheses, 17, 55 (1937).

Apparently, not all esters having hydrogen on the α -carbon atom undergo the acetoacetic ester condensation to form β -ketoesters. Thus, ethyl dichloroacetate when treated with alcoholic sodium ethoxide yields ethyl oxalochloroacetate diethyl acetal and ethyl diethoxyacetate. It Although methyl diphenylacetate is converted by triphenylmethylsodium into its sodium enolate (which may be condensed with acid chlorides to form β -ketoesters), the self-condensation of this ester apparently has not been effected. The unsaturated esters, ethyl acrylate 18 and ethyl crotonate, when treated with sodium ethoxide, undergo condensations of the Michael type; however, as indicated above, ethyl crotonate undergoes the acetoacetic ester reaction with certain esters (ethyl oxalate and ethyl formate).

Phenyl acetate fails to condense in the presence of sodium phenoxide." Although purely aliphatic alkyl acetates (in which the alkyl group is methyl, ethyl, propyl, etc.), undergo the normal acetoacetic ester condensation when treated with the corresponding sodium alkoxide (or with metallic sodium), the phenyl-substituted alkyl acetates, benzyl and benzohydryl acetates (and also allyl and cinnamyl acetates) undergo socalled abnormal acetoacetic ester reactions. Thus, benzyl acetate with sodium benzyloxide yields only traces of benzyl acetoacetate,21 and when heated with metallic sodium this ester yields the "alkylated" product, β-phenylpropionic acid; 2. 2 allyl acetate with sodium undergoes the same type of reaction. Benzohydryl acetate and sodium yield still another "abnormal" product, tetraphenylethane; a cinnamyl acetate undergoes the same type of reaction.2 Benzohydryl acetate with sodium benzohydryloxide yields the "alkylated" product, 8.8-diphenylpropionic acid, and other products.21 It should be pointed out that these so-called abnormal acetoacetic ester reactions presumably require relatively high temperatures (100-300°) and that at least benzyl acetate undergoes the normal acetoacetic ester condensation when treated with triphenylmethylsodium at room temperatures.24

Side Reactions

The most important type of side reaction that is encountered when the acetoacetic ester condensation is carried out involves the reaction of the

¹⁷ Cope, J. Am. Chem. Soc., 58, 570 (1935).

¹⁴ Pechmann and Rohm, Ber., 34, 428 (1991).

¹³ Pechmann and Rohm, Ber., 33, 3324 (1909).

^{*} Fisher and McElvain, J. Am. Chem. Soc., 55, 1765 (1934).

²¹ Bacon, Am. Chem. J., 33, 68 (1995).

²² Conrad and Hodgkinson, Ann., 193, 298 (1978).

²² Tseou and Wang, J. Chinese Chem. Sec., 5, 224 (1937).

²⁴ Hudson and Houser, unpublished observations.

carbonyl group of the ester with the base used as condensing agent: indeed, this type of reaction is frequently the most characteristic reaction of the ester. Sodium alkoxides may react reversibly with the carbonyl group of the ester.

$$RCH_1CO_2C_1H_4 + X_3OC_2H_4 \rightleftharpoons RCH_2C + OC_2H_3$$

$$OC_2H_4$$

However, other bases of sufficient strength to ionize the α-hydrogen of esters and effect condensations are also capable of reacting irreversibly with the carbonyl group of esters. Thus, sodium amide effects the ammonolysis of esters," and Grignard reagents react with esters to form ketones or earlings.

These reactions generally predominate, but sodium (or potassium) amide and certain Grignard reagents react preferentially with the a-hydrogen of certain esters and effect condensations. Although triphenylmethylsodium is capable of reacting with the carbonyl group of esters, this type of reaction occurs apparently only when the ester contains no a hydrogen; for example, with methyl benzoate a ketone is formed,26

$$\mathrm{C_{6}H_{6}CO_{2}CH_{3} + (C_{6}H_{6})_{3}CN_{5} \rightarrow \mathrm{C_{6}H_{5}COC(C_{6}H_{6})_{3} + N_{8}OCH_{3}}$$

Metallic sodium is capable of reacting with the carbonyl group of esters to form acyloins 17 (RCHOHCOR) and diketones 17 (RCOCOR), but in the presence of excess of ethyl acctate or ethyl propionate, metallic sodium effects only the acetoacetic ester condensation.18 With ethyl n-butyrate or ethyl isobutyrate and sodium, however, the acetoacetic ester condensation does not take place even in the presence of an excess of the ester; instead, acyloins, diketones, and higher-boiling products are formed.28

In certain cases, side reactions involving the alcohol portion of the ester are encountered. Thus, in the presence of potassium amide in liquid

²⁵ See Bergstrom and Fernehus, Chem. Rev., 12, 142-150 (1933), ibid., 20, 459 (1937). 34 Schlenk and Cehs. Ber., 49, 610 (1916).

¹⁷ Bouveault and Locquin, Bull. no. chim., [3] 35, 629 (1906).

¹⁸ Snell and McElvain, J. Am. Chem. Soc. 53, 750 (1931).

ammonia, β -phenylethyl acetate is converted partly to styrene.²⁹ The so-called abnormal acetoacetic ester reactions discussed above (p. 272) may also be regarded as other types of side reactions involving the alcohol portion of the ester.

Cyclizations (Dieckmann reaction)

Certain esters having hydrogen on the & or & carbon atom which is activated (generally by a carbonyl group) undergo intramolecular cyclization. These reactions may be illustrated by the formation of 2-carboethoxycyclopentanone from ethyl adipate.

Similarly, ethyl pimelate can be eyelized to a eyelohexanone derivative, but ethyl subcrate affords 2-carboethoxycycloheptanone in low yield. The esters of glutaric, azelaic, and sebaeic acids fail to cyclize intramolecularly in the presence of sodium ethoxide.

This cyclization has proved particularly useful in preparing polycyclic compounds. For example, the cyclic ketoester which is an intermediate in the synthesis of the sex hormone equilenin can be obtained in practitically quantitative yield.²⁷

$$\begin{array}{c} \text{CH}^{\text{i}}\text{CO}^{\text{i}}\text{CH}^{\text{i}} & \begin{array}{c} \text{CH}^{\text{i}}\text{CH}^{\text{i}} & \text{CH}^{\text{i}}\text{CH}^{\text{i}} \\ \text{CO}^{\text{i}}\text{CH}^{\text{i}} & \begin{array}{c} \text{CH}^{\text{i}} & \text{CH}^{\text{i}} & \text{CH}^{\text{i}} \\ \text{CH}^{\text{i}} & \text{CO}^{\text{i}}\text{CH}^{\text{i}} \\ \end{array}} & \begin{array}{c} \text{CH}^{\text{i}}\text{CH}^{\text{i}} & \text{CH}^{\text{i}}\text{CH}^{\text{i}} \\ \text{CH}^{\text{i}} & \text{CO}^{\text{i}}\text{CH}^{\text{i}} \\ \end{array}} & \begin{array}{c} \text{CH}^{\text{i}}\text{CH}^{\text{i}} & \text{CH}^{\text{i}}\text{CH}^{\text{i}} \\ \text{CH}^{\text{i}} & \text{CH}^{\text{i}}\text{CH}^{\text{i}} \\ \end{array}} & \begin{array}{c} \text{CH}^{\text{i}}\text{CH}^{\text{i}} & \text{CH}^{\text{i}} \\ \end{array}} & \begin{array}{c} \text{CH}^{\text{i}} & \text{CH}^{\text{i}} \\ \end{array}} & \begin{array}{c} \text{CH}^{\text{i}} & \text{CH}^{\text{$$

Certain intramolecular cyclizations are accompanied by decarboxylation, illustrated as follows.

²³ Skell and Hauser, unpublished observations.

²⁰ Bachmann, Cole, and Wilds, J. Am. Chem. Soc., 62, 835 (1949).

Five- and six-membered rings may also be formed by intermolecular condensation and cyclization, examples of which may be represented as follows:

$$\begin{array}{c} \text{CO}_{1}\text{C}_{2}\text{H}_{4} \\ \text{CH}_{2}\text{CO}_{2}\text{C}_{2}\text{H}_{4} \\ \text{CH}_{3}\text{CO}_{2}\text{C}_{2}\text{H}_{4} \\ \text{CH}_{4}\text{CO}_{2}\text{C}_{2}\text{H}_{4} \\ \text{CO}_{4}\text{C}_{3}\text{H}_{4} \\ \text{CH}_{4}\text{CO}_{2}\text{C}_{3}\text{H}_{4} \\ \text{CH}_{4}\text{CO}_{2}\text{C}_{3}\text{H}_{4} \\ \text{CH}_{4}\text{CO}_{2}\text{C}_{3}\text{H}_{5} \\ \text{CH}_{2}\text{CO}_{2}\text{C}_{3}\text{H}_{5} \\ \text{CO}_{3}\text{C}_{2}\text{H}_{5} \\ \text{CO}_{3}\text{C}_{2}\text{H}_{5} \\ \text{CO}_{4}\text{C}_{2}\text{H}_{5} \\ \text{CO}_{4}\text{C}_{2}\text{H}_{5} \\ \text{CO}_{5}\text{C}_{2}\text{H}_{5} \\ \text{CO}_{5}\text{C}_{5}\text{H}_{5} \\ \text{CO}_{5}\text{C}_{5}\text{C}_{5}\text{C}_{5} \\ \text{CO}_{5}\text{C}_{5}\text{C}_{5} \\ \text{CO}_{5}\text{C}_{5}\text{C}_{5} \\ \text{CO}_{5}\text{C}_{5}\text{C}_{5} \\ \text{CO}_{5}\text{C}_{5}\text{C}_{5} \\ \text{CO}_{5}\text{C}_{5}\text{C}_{5} \\ \text{CO}_{5}\text{C}_{5}\text{C}_{5} \\ \text{CO}_{5}\text{C}_{5}

The Acylation of Esters with Acid Chlorides

Closely related to the acylation of esters with esters (as occurs in the acetoacetic ester reaction) is the acylation of esters with acid chlorides or anhydrides. For example, ethyl isobutyrate in the form of its sodium coulote (prepared from the ester and triphecylmethylsodium) may be acplated not only with ethyl benzoste **or phenyl benzosta**, but also acylated not only with ethyl benzoste **or phenyl benzosta**, but also with benzole anhydride **in obenzol etholoide; **n the reactions with the last three reagents (especially the one with the acid chloride), being essentially irreversible, give the best yield of ethyl benzyldimethylace essentially irreversible, give the best yield of ethyl benzyldimethylace that. These reactions may be represented by the following general equatate. These reactions may be represented by the following general equa-

¹¹ Hudson, Dick, and Hauser, J. Am. Chem. Soc., 60, 1960 (1938).

tion in which X represents ethoxide, phenoxide, benzoate, or chloride groups.

$$C_6H_6COX + Na[C(CH_3)_2CO_2C_2H_5] \rightarrow C_6H_6COC(CH_3)_2CO_2C_2H_5 + NaX$$

The reactions of the sodium enolates of ethyl isobutyrate and other esters of disubstituted acetic acids with various acid chlorides are of particular value for the preparation of α , α -disubstituted β -ketoesters ¹⁵ of the typc RCOCR₂CO₂C₂H₅. The acylation of the sodium enolate of ethyl acetate with acid chlorides does not stop with monoacylation but produces mainly the diacylated acetate ¹⁵ (RCO)₂CHCO₂C₂H₅.

EXPERIMENTAL PROCEDURES

Choice of Base

The base most commonly used for the acetoacetic ester condensation is the sodium alkoxide that corresponds to the alcohol portion of the ester; for example, sodium ethoxide is used with ethyl esters. These bases are generally readily available and usually they produce no byproducts except the corresponding alcohol, which is easily separated from the condensation product. Under the proper conditions, sodium alkoxides effect the condensation of acetates and most esters that have two hydrogens on the α -carbon atom (in reactions of either two similar or two different ester molecules); two such esters, however, ethyl isovalerate and ethyl t-butylacetate, as well as esters that have only one α -hydrogen atom (e.g., ethyl isobutyrate as) fail to condense in the presence of sodium ethoxide.

The second most useful base is triphenylmethylsodium, which condenses not only ethyl acetate ¹⁴ and presumably all esters that are condensed by sodium alkoxides, but also certain esters that cannot be condensed by means of the latter bases. Thus, triphenylmethylsodium effects the self-condensations of ethyl isovalerate ¹⁵ and ethyl isobutyrate ² and the mixed ester condensations between ethyl isobutyrate and esters with no α-hydrogen, for example, ethyl oxalate. Also, triphenylmethylsodium is the only base that has been found to be generally satisfactory for the condensations of esters with acid chlorides. With the proper equipment, triphenylmethylsodium is readily prepared, and it generally produces no appreciable amounts of by-products except triphenylmethane, which usually may be separated readily from the condensation product.

²³ McElvain, J. Am. Chem. Soc., 51, 3124 (1929).

³² Roberts and McElvain, J. Am. Chem. Soc., 59, 2007 (1937).

Mesitylmagnesium bromide 24 effects the self-condensation of ethyl isovalerate and ethyl isobutyrate (and also ethyl t-butylacetate). but the yields of products are not so high as those obtained with triphenylmethylsodium. Apparently, mixed ester condensations have not been attempted with mesitylmagnesium bromide, but it seems likely that at least certain of them might be effected; however, an attempt to condense ethyl isobutyrate with benzoyl chloride by means of mesitylmagnesium bromide has been unsuccessful 15

Certain other bases have limited application. Although isopropylmagnesium bromide is not satisfactory for the self-condensation of ethyl acctate or ethyl isovalerate,24 this Griguard reagent does bring about the self-condensations of ethyl phenylacetate 25 (in which the ce-hydrogen is activated by the phenyl group) and of t-butyl acetate 24 (in which the carbonyl group is deactivated by the t-butyl group). Also, potassium amide effects the self-condensation of Lbutyl acetate, to but sodium amide reacts with ethyl acetate to give only a low yield of acetoacetic ester 35 and with ethyl isobutyrate to give little or none of the β-ketoester." Sodium amide is satisfactory, however, for the cyclization of ethyl adipato 35 (and especially for various ketone-ester Claisen condensations).10 Sodium n-amylacetylido, NaC=C-(CH2),CH3, has been used for the self-condensation of certain esters.**

In general, the appropriate sodium alkevide would be chosen for a condensation if it is capable of effecting the reaction; if not, triphenylmethylsodium would be chosen unless the triphenylmethane produced is difficult to separate from the condensation product, and in that case. mesitylmagnesium bromide would be tried. In special cases, other bases may be chosen; thus for the self-condensation of ethyl phenylacetate, isopropylmagnesium bromide 15 would be used instead of sodium ethoxide, 2 since a considerably better yield of condensation product is obtained with the Grignard reagent. For the self-condensation of t-butyl acetate, triphenylmethylsodium,14 potassium amide,24 or isopropylmagnesium bromide 24 may be chosen instead of sodium t-butoxide, since the first two bases give as good or better yield of condensation product and this particular sodium alkoxide is rather difficult to prepare; 20 the yield of product with the Grignard reagent is slightly lower than yields obtained with the other bases.

No. 14 Spielman and Schnudt, J. Am. Chem. Soc., 53, 2009 (1937).

³ Conant and Biatt, J Am. Chem. Soc. 81, 1227 (1929).

at Titherly, J. Chem. Soc., \$1, 1920 (1982). Freund and Speyer, Ber., \$5, 2321 (1902). 47 Scheibler and Stein, J. prakt. Chem., 139, 107 (1934)

n Haller and Cornubert, Bull soc. chim. [4] 39, 1626 (1926); Compt. rend., 179, 315

¹⁹ Moureu and De Lange, Bull. soc. chim., [3] 27, 373 (1902). (1924).

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reactions generally increases the yields of \$\beta\$-ketoesters. These "forced" reactions are of particular value for the self-condensation of ethyl n-valerate and higher esters; "the lower esters distil with the alcohol and must be used in considerable excess. 23

The condensation of two different esters is sometimes carried out by first mixing the acylating ester (which should be incapable of self-condensation) with sodium ethoxide and then adding the other ester and heating the mixture. When an ester tends to condense with itself as readily as with the acylating ester, the yield of mixed-ester condensation product may be improved by adding simultaneously to the acylating ester, at intervals, small portions of the ester to be acylated and approximately equivalent amounts of metallic sodium. Ethyl benzoylacetate is prepared commercially essentially according to this scheme. Also, this procedure is successful for the acylation of ethyl acetate with ethyl diethoxyacctate; " this reaction is one of the few examples in which two esters both of which have a hydrogen can be condensed satisfactorily.

Several procedures have been chosen to illustrate the various techniques and to illustrate the following types of reactions: self-condensation of esters; mixed-ester condensation; intramolecular cyclization; intermolecular self-condensation and cyclization; intermolecular mixedester condensation and cyclization. Also, the preparations of powdered sodium and of alcohol-free sodium ethoxide are described.

PROCEDURES

Powdered Sodium." Freshly cut sodium is covered with about ten times its weight of tylene (preferably purified with sodium) in a roundbottomed flask equipped with a reflux condenser, and the mixture is heated until the xylene boils and the sodium melts. The flask is stonpered with a cork, wrapped with a towel, and shaken vigorously while the sodium resolidifies. In this manner, as much as 50-60 g of sodium may be converted into a very fine powder. The xylene may then be decanted and replaced with another inert solvent.

Alcohol-Free Sodium Alkoxides.4 Powdered sodium is covered with approximately ten times its weight of inert solvent (purified xylene, benzene, ether, or ligroin) in a flask equipped with a mechanical stirrer, dropping funnel, and a reflux condenser carrying a soda-lime tube. The calculated amount of absolute alcohol (1 mole to 1 gram atom of sodium)

⁴³ Briese and McElvain, J. Am. Chem. Soc., \$5, 1697 (1933).

⁴² Dakm and Dodley, J. Chem. Soc., 195, 2455 (1911). Johnson and Cretcher, J. Am. Chem. Soc . 37. 2149 (1915); Johnson and Mikeska, shid . 41, 812 (1919).

⁴ Houben-Weyl, Vol 11 1925, p. 748.

is diluted with twice its volume of the inert solvent and added dropwise to the vigorously stirred contents of the flask. When the initial reaction subsides, nearly all the sodium has reacted. The mixture is then refluxed with continuous stirring until the sodium has completely disappeared. The solvent may then be distilled, the last traces being removed under reduced pressure.

Sodium methoxide and sodium ethoxide may be prepared in this manner, but the method is not satisfactory for sodium alkoxides higher than sodium ethoxide; methods of preparation of higher alkoxides are described in the literature.

Ethanol-free sodium ethoxide may also be prepared by adding freshly cut sodium to an excess of absolute ethanol contained in a round-bottomed flask which is immediately connected to a condenser set downward for distillation and to a source of dry nitrogen; a filter flask to which a soda-lime tube is attached is used as a receiver. When the reaction has ceased the excess ethanol is removed by distillation. Dry nitrogen is then admitted and the flask is heated in an oil bath at 150°/20 mm. for one hour. Before use the white cake of sodium ethoxide should be pulverized by stirring or shaking in an atmosphere of nitrogen.

Self-Condensation of Various Alkyl Acetates,²² Ethyl Propionate,²² and Ethyl Butyrate ²² in the Presence of Sodium Alkoxides. The self-condensation of ethyl acetate by means of sodium is described in detail in *Organic Syntheses*.⁴³ The following procedure, involving sodium alkoxides, may be applied to a variety of esters of acetic acid as well as to the ethyl esters of propionic and butvric acids.

In a 500-cc. three-necked flask, fitted with a stirrer, reflux condenser, and a thermometer which dips below the surface of the reaction mixture, are placed 0.2 mole of the alcohol-free alkoxide and 1.2 moles of the corresponding ester. The contents of the flask are heated with stirring to the temperature and for the time indicated in Table I. At the end of the reaction time the flask is surrounded by ice and the reaction mixture is cooled to 10° . The reflux condenser is replaced by a dropping funnel, and 36 g. of 33.3% aqueous acetic acid is added dropwise to the mixture at such a rate that the temperature remains below 15° . When the solid material has completely dissolved, the ester layer is separated and the aqueous layer is extracted with four 50-cc. portions of ether. The combined ester layer and ether extracts, after drying over anhydrous sodium sulfate, is fractionally distilled. The conditions of reaction, the maximum yields, and the boiling points of various β -ketoesters obtained are given in Table I.

⁴⁵ Inglis and Roberts, Org. Syntheses, Coll. Vol., 1, 230 (1932).

TABLE I
SELF-CONDENSATION IN THE PRESENCE OF SOUTH ALKOYIDES

Ester Used	Temperature	Time of	Pre	oduet
Ester Used	of Reaction, °C.	Reaction, hr.	Yield, %	B p./mm.
Ethyl acetate	78	8	75-76	78-80/16
Ethyl propionate	95	t6	46-47 4	88-90/12
Ethyl n-butyrate	95	32	40-42	102-105/12
Methyl acetate	57	t6-32	57-61	-
n-Propyl acetate	77	16	73	78/11
n-Butyl acetate	115	8	71	90/11
Isobutyl acetate	tt5	4 5	71	84 5/11
Isopropyl acetate	87	8	75	69/11
8-Butyl acetate	87	8	80	79 t/11
i-Butyl acctate	77	32	52	71 5/11

a A higher yael of the Accessive a obtained by persodic destillations of portions of the sater together with the also high that is formed denoisy the reaction, (see following procedure), but considerable access of the pure enter as required in the process.
Breatton matrices have all all 15 for four hours and then allowed to stand at more improved in fact.

Forced Self-Condensation of Ethyl Esters of n-Valeric and Higher Aliphatic Acids " in the Presence of Sodium Ethoxide. In a 125-cc. modified Claisen flask with a fractionating side arm 35 cm. long are placed 0.1 mole of the purified ester and 0.05 mole of ethanol-free sodium ethoxide (prepared from absolute ethanol and powdered sodium under dry ether, p. 279). The reaction flask is attached to the receiving flask (which is not cooled), and this flask in turn is attached through a sodalime tower and a safety bottle to a manometer and a water pump. The safety bottle contains a stoprock which can be opened to the air and by which the pressure in the system can be regulated. The reaction flask is then heated carefully in an oil bath to a temperature and under a pressure that cause a moderate, but not too vigorous, evolution of ethanol vapor as shown by the coulition of the reaction mixture. The required temperature and pressure vary with the boiling point of the ester, the more volatile ones requiring lower reaction temperatures and higher pressures in order to avoid loss of ester. Consequently the time neces-Sary for the completion of the reaction in these cases is increased. A summary of the conditions for the reaction of the various esters is given in Table II. Column 2 shows the temperatures and column 3 the pressures which are most satisfactory at the beginning of each reaction to casure a moderate evolution of alcohol. After the reaction has pro-

b Reaction mixture heated at 115° for four hours and then allowed to stand at room temperature for tasks hours.

ceeded for some time the temperature and pressure can be raised and lowered, respectively, without appreciable loss of ester. Column 4 gives the time required for completion of the reaction; at the end of this period the reaction mass ceases ebullition. The reaction product after cooling is treated with the calculated quantity of 30% acetic acid and shaken vigorously until the sodium salt is completely decomposed. The ketoester is then extracted with 25 cc. of benzene, and the resulting benzene solution, after washing with water, is dried over anhydrous sodium sulfate. The benzene is removed by distillation. Ethyl α -lauryllaurate and ethyl α -myristylmyristate are recrystallized from absolute methanol. The liquid products are purified by distillation. This procedure is quite satisfactory for all the ketoesters except ethyl a-pelargonylpelargonate and ethyl a-caprylcaprate, both of which suffer a small amount of pyrolysis to the corresponding ketone, which appears as a low-boiling solid fraction in the distillate. The yields and boiling (or melting) points of the β -ketoesters are shown in Table II (last column).

TABLE II CONDITIONS AND TIME REQUIRED FOR FORMATION OF β -Ketoesters RCH₂COCH(R)CO₂C₂H₅

	Reaction	Reaction	Time for	K	etoester
Ester Used, Ethyl	Temperature, °C.	Pressure, mm.	Completion, hr.	Yield,	B.p./mm. or m.p., ° C.
Valerate	89-90	120-130	7-8	77	109-110/5
Caproate	90-95	75-80	7-8	80	132-133/5
Heptoate	90-95	60-65	7	78	147-148/5
Caprylate	90-95	20-25	5	84	173-175/5
Pelargonate	100~105	15-20	4-5	74	195-200/5
Caprate	105-110	15-20	4	74	220-225/5
Laurate	120-125	15-20	4	79	28-29
Myristate	125-130	15-20	4	84	(m.p.) 37–38 (m.p.)

Condensation of Two Different Esters 46 in the Presence of Sodium. Preparation of Ethyl γ,γ -Diethoxyacetoacetate 43 and Ethyl Benzoylacetate. 40,47 In a three-necked flask fitted with a stirrer, a dropping

⁴⁵ For a detailed procedure for the condensation of ethyl oxalate with ethyl propionate in the presence of sodium ethoxide, see Cox and McElvain, Org. Syntheses, 17, 54 (1937).
47 Yuoh Fong Chi and Yung Mao Lee, Trans. Science Soc. China, 8, 87-89 (1934).

funnel, and a reflux condenser carrying a calcium chloride tube, 86 g. (0.49 mole) of ethyl diethoxyacetate is heated to 85-90° and portions of 2 g. of sodium wire and 9 cc. of ethyl acetate are added at half-bour intervals until 34 g. (1.5 atoms) of sodium and 130 g. (1.5 moles) of ethyl acctate have been introduced. The reaction is quite vigorous at first, but after it subsides the sodium and ethyl acetate can be added a little more rapidly; the seventeen additions can be made in about six hours. The brown, viscous reaction mixture is stirred continuously, and stirring and heating at 85-90° are continued for four hours after the last addition of sodium and ethyl acetate. Ethanol (30 cc.) is added to dissolve the residual sodium, and then the oil, cooled somewhat but not allowed to become too viscous, is poured into a mixture of 130 cc. of concentrated hydrochloric acid and 130 g. of ice. The oily layer is immediately separated, and the aqueous layer is extracted once with a small quantity of other. The oily layer and other extract are combined, washed with sodium carbonate solution, dried, and the ether and ethanol distilled on a bath at 100°. Fractional distillation of the residue gives 76 g. (71%) of othyl 7,7-diethoxyacotoacetate boiling at 112°/4-6 mm. A considerable amount of ethyl acctoacetate passes over in the fore-run, along with some ethyl diethoxyacetate.

By a similar procedure ethyl benzoylacetate is obtained in 55-77% yield from ethyl acetate, ethyl benzoate, and sodium.47 Ethyl benzoylacctato is prepared commercially essentially in this manner " in a yield of 68%; much ethyl acetoacetate is also obtained in the same reaction.

By a similar procedure methyl benzoylacetate is obtained in 45-85% yield from methyl acetate, methyl benzoate, and sodium. 45 The method is not very satisfactory, however, for the acylation of ethyl

acetate with its purely aliphatic homologe 48

Self-Condensation Followed by Cyclization. Preparation of Ethyl Succinylsuccinate by the Use of Sodium Ethoxide to or Sodium. To 29 g. (0.43 mole) of ethanol-free sodium ethovide covered with 140 cc. of dry ether is added 38 g. (0.21 mole) of ethyl succinate. The mixture is refinzed three or four days. The other is then distilled and the residue is neutralized in the cold with dilute sulfuric acid. The crude crystalline ester is collected and washed with water. It is dissolved in 200 cc. of

Wahl and Doll, Bull. sec chim. [4] 13, 265 (1913). Wahl, viol., [4] 3, 946 (1908).

⁶ For the cyclustion of a number of erters of polyfunctional acids, see Dieckmann, Wahl and Meyer, thid . [4] 3, 957 (1908) Ann., 317, 51 (1901), for a detailed procedure for the cyclication of ethyl adipate, see (a) Pinkney, Org. Syntheses, 17, 30 (1937), and (b) Lanstend and Meade, J. Chem. Soc. 940 (1934).

¹⁴ Prutti, Gart. chim. stal . 20, 167 (1990). " Uponski and Turin, Chem. Zentr , III, 754 (1923).

95% ethanol, decolorized with 1 g. of charcoal, and allowed to erystallize. The yield of ethyl succinylsuccinate, m.p. 126-127°, is about 60%.

When sodium is used, the procedure involves the addition of a slight excess of powdered ⁵² sodium (27 g., 1.17 atom) to ethyl succinate (75 g., 0.43 mole) containing a small amount (4 cc.) of absolute ethanol. After the initial reaction, which may require cooling to prevent flooding of the reflux condenser, the mixture is heated to 60° for five hours, then to 100° for two hours, and finally to 110° for twenty-five hours. It is then cooled, added cautiously to cold dilute sulfuric acid, and worked up as just described; the yield is about 60%.

Condensation of Two Different Esters Followed by Cyclization-Preparation of 3,5-Dicarboethoxycyclopentanedione-1,2.¹³ To 34 g. (0.5 mole) of ethanol-free sodium ethoxide, covered with 200 ee. of anhydrous ether and contained in a flask fitted with a reflux condenser, is added 36.5 g. (0.25 mole) of ethyl oxalate. After mixing thoroughly, 47 g. (0.25 mole) of ethyl glutarate is added over about fifteen minutes and the mixture is heated to refluxing. After approximately one hour, when solution is complete, the ether is distilled and the residue is heated to 120-130° until it changes to a yellow solid (about three hours). The reaction mixture is cooled and washed with ice-cold dilute sulfurie acid (10%), then with ice-water. After drying in the air (twenty-four hours) the crude product, m.p. 90-104°, weighs 43 g. It is recrystallized from 80 ee. of 95% ethanol, and 30 g. (50%) of pure material (m.p. 115°) is obtained.

It is reported that ethyl β -methylglutarate condenses with ethyl oxalate to give an almost quantitative yield ⁵³ of 4-methyl-3,5-dicarboethoxyeyclopentanedione-1,2, melting at 108°, and that ethyl β -phenylglutarate with ethyl oxalate gives an excellent yield ⁵³ of the 4-phenyl derivative, m.p. 160-161°. Ethyl β , β -dimethylglutarate with ethyl oxalate gives only a low yield ⁵³ of the 4,4-dimethyl derivative by this procedure, but a considerably better yield is obtained using the corresponding methyl esters and sodium methoxide. ⁵⁴

Selection of Experimental Conditions with Triphenylmethylsodium

The first step in procedures for carrying out self-condensations of esters, mixed ester condensations, or ester acid chloride condensations by means of triphenylmethylsodium consists in converting the ester to be acylated into its sodium enolate. This is done simply by adding the

⁵² Jeaurenaud, Ber., 22, 1282 (note 4) (1889).

⁵³ Dieckmann, Ber., 32, 1930 (1899); Ber., 27, 965 (1894).

⁵⁴ Komppa, Ann., 368, 137 (1909).

ester to an equivalent amount of triphenylmethylsodium in ether solution. The formation of the enolate is indicated by the fading or disappearance of the characteristic deep red color of the base. Self-condensation of the ester is effected merely by allowing the enolization mixture to stand, usually at room temperature; the enolate anions are acylated by molecules of unchanged ester with which they are in equilibrium. The acylation of the sodium enolate with other esters or with acid chlorides is effected by adding an equivalent amount of the reagent to the enolization mixture as soon as the characteristic deep red color of the triphenylmethylsodium has nearly or completely disappeared; in this way, self-condensation of the original ester is minimized. The acylation of an ester by another ester or acid chloride will, of course, be successful only when this reaction takes place more rapidly than the selfcondensation of the original ester. The reaction mixtures are worked up by first neutralizing them (except when acid chlorides are used) with acetic acid, and extracting the mixture with water. The ether solution (which may be washed with sedium bicarbonate solution) is dried and the other is distilled. The β -ketoester is isolated from the residue (mainly triphenylmethane) by fractional distillation in vacuum. If the product is a high-boiling liquid (b.p. above 150°/15 mm.), triphenylmethane should be removed before fractionation by cooling and seeding the residue; the solubility of the triphenylmethane is greatly reduced by the addition of one or two volumes of 95% ethanol. Techniques other than distillations may be employed in the isolation of crystalline products or of alkali-soluble products.

The time required for the conversion of an ester into its sodium enolate varies greatly with different esters. For example, with ethyl acetate, the color of the triphenylmethylsodium disappears almost immediately even when the reaction is carned out at 0°, but with ethyl isobutyrate the color changes to light red only after a few minutes at room temperature, while with ethyl diethylacetate there is no noticeable decrease in the depth of color until after a few hours at room temperature. Also, the time required for completion of the acylation varies greatly. For example, the self-condensation of ethyl acetate is practically complete within an hour (a 43% yield of ethyl acetoacetate is obtained within three minutes at room temperature), a but the self-condensation of ethyl isobutyrate 2 or ethyl isovalerate 15 requires a day or longer. Acylations of the sodium enolates of esters with acid chlorides or with especially reactive esters such as ethyl oxalate are essentially complete within a few minutes.15 Although considerable heat is generated in the rapid reactions, no special cooling arrangements are necessary when the triphenylmethylsodium is used in approximately 0.15 molar concentrations (or

less) and at an initial temperature of approximately 20° or less. With more concentrated solutions or when the room temperature is high, the reaction mixture should be cooled by means of an ice bath.

Triphenylmethylsodium is conveniently prepared in almost quantitative yield (90%) by shaking a solution of pure triphenylchloromethane (m.p. 112-113°) in dry ether with an excess of freshly prepared sodium amalgam. Since the base reacts readily with active hydrogen compounds (water, ethanol, etc.) and with oxygen, the materials should be pure and the base should be prepared and used in an atmosphere of dry nitrogen. The base is commonly prepared and used in approximately 0.15 molar concentrations; however, concentrations up to 0.5 molar have been employed.

Procedures have been chosen to illustrate the preparation of triphenylmethylsodium, the self-condensation of an ester, and a mixed ester condensation. An ester acid-chloride condensation is described in detail in Organic Syntheses; 8 the reaction on a larger scale is described in the literature. 15

Procedures

Triphenylmethylsodium. 55, 15 Nine hundred and fifty grams of 1.5% sodium amalgam is prepared in the following manner. In a 250-cc. Pyrex Erlenmeyer flask 14 g. (0.61 atom) of freshly cut sodium is covered to a depth of 2 cm. with high-boiling mineral oil. The flask is heated until the sodium begins to melt. Then 935 g. of mercury, contained in a separatory funnel whose stem passes through a cardboard shield (8 cm. square), is added rapidly to the molten sodium (hood!). The flask is stoppered and shaken until no solid particles of amalgam remain. When the flask has cooled to approximately 80°, or when the amalgam first begins to crystallize, the flask is cooled rapidly to room temperature by swirling in cold water. The oil is decanted, and the amalgam (950 g.) is washed twice with dry benzene or ligroin.

To a mixture of 70 g. (0.25 mole) of triphenylchloromethane (m.p. 112–113°) and 950 g. of freshly prepared 1.5% sodium amalgam in a 2-l. Pyrex glass-stoppered bottle, 1500 cc. of absolute ether is added. The glass stopper is lubricated with a little Lubriseal and firmly inserted. The bottle is clamped securely in a mechanical shaker which makes a 4- to 5-in. stroke and three to four strokes a second. Shaking is begun; if the temperature of the bottle rises above approximately 40°, shaking is interrupted until the bottle cools somewhat. The characteristic deep red color appears after five to fifteen minutes' shaking. After shaking for three to six hours the bottle is cooled to room temperature and

⁵⁵ Renfrow and Hauser, Org. Syntheses, 19, 83 (1939).

removed from the shaker. The stopper is clamped down and the mixture allowed to stand undisturbed overnight. Sodium chloride and particles of mercury settle to the bottom.

The solution is analyzed in the following way. A tube delivering a rapid stream of dry nitrogen is held at the mouth of the bottle while the stopper is loosened and slowly removed. A sample is taken in the conventional manner, by means of a 25-ce, pipette, and delivered into a small separatory funnel containing 25 ce, of distilled water. (The bottle should be restoppered immediately.) The separatory funnel is stoppered and shaken. The aqueous layer is drained into a 250-ce. Erlenneyer flask, and the ether layer is extracted with two additional 25-ce, portions of distilled water. The combined aqueous extracts are titrated with 0.2 N sulfuric acid, methyl red being used as the indicator. The average concentration of the triphenylmethyl sodium is 0 14 to 0 15 mole per liter.

The solution is transferred to a nitrogen-filled 2-1. Erlenmeyer flask by means of a pressure siphon, using nitrogen gas under limited pressure (40–80 mm.). For convenience, the receiving flask should be graduated, and the siphon tube provided with a stopcock. A plug of cotton packed and the siphon tube provided with a stopcock. A plug of cotton packed recent the diffusion of air into the flask. By carefully adjusting the depth to which the siphon tube extends into the bottle, it is possible to transfer to which the siphon tube extends into the bottle, it is possible to transfer the sludge from the botton of the bottle. When the transfer is complete, the receiving flask is stoppered tightly. The solution should then be used within a few minutes. The quantity of base available for use is usually 0.20–0.21 mole (80–85%).

By using solid sodium amalgam (3%), much higher concentrations of the base may be prepared without special cooling. The modifications necessary in the preparation of approximately 1 mole of triphenylmentysodium are given below.

The 3% sodium amalgam prepared as described above from 51 g, of sodium and 1649 g, of mercury is poured while hot into a shallow iron pan and allowed to cool. The mineral oil is decanted, and, by means of a hammer and chiest, the amalgam is broken into pieces measuring about hammer and chiest, the amalgam is washed thoroughly with benzene 1 cm. on each edge. The amalgam is washed thoroughly with benzene 1 cm. on each edge. The amalgam is washed thoroughly with benzene the ligroin and transferred to a 2.1. Pyrcx bottle. A solution of 278 g. of ligroin and transferred to a 2.1. Pyrcx bottle. A solution of 278 g. of the prepared and shaken in the manner either is added, and the bottle is stoppered and shaken in the manner already described. The shaking process should be watched very closely and interrupted whenever necessary in order to avoid overheating. The and interrupted whenever necessary in order to avoid overheating. The

ing; little heat is generated after the appearance of the color. Shaking is continued until no pieces of solid amalgam remain, and then for two hours longer. The bottle is cooled, removed from the shaker, and allowed to stand, as described above. The solution is then analyzed, by removing a 10-cc. aliquot and diluting with 25 cc. of ether before extraction and titration.

Except when alkylations are to be carried out, it is frequently permissible to use the solution of triphenylmethylsodium without separating it from the sludge of sodium chloride and amalgam. The total volume of solution may be considered to be equal to the volume of the ether employed plus 0.77 cc. per g. of triphenylchloromethane used. When the solution is not separated from the amalgam and when the above volume correction is applied in the calculation of the quantity of base available, yields of 85–93% of the theoretical amount are obtained.

Self-Condensation. Ethyl a-Isovalervlisovalerate. To a solution of 0.21 mole of triphenylmethylsodium in approximately 1400 cc. of ether contained in a 2-l. Erlenmeyer flask, is added 31.8 cc. (27.5 g., 0.21 mole) of ethyl isovalerate (b.p. 134-135°). The flask is stoppered well, shaken to effect complete mixing, and allowed to stand at room temperature for sixty hours. The reaction mixture is then acidified by the addition, with shaking, of 15 cc. (approximately 0.25 mole) of glacial acetic acid. The mixture is extracted with 100 cc. of water. The resulting ether solution is washed with 50-cc. portions of 10% sodium carbonate solution until The ether solution is dried by shaking with free from excess acid. anhydrous sodium sulfate and allowing to stand over Drierite. solution is filtered and the ether distilled on a water bath. The residue is distilled in vacuum. The fraction boiling up to 170°/15 mm. is redistilled through a 6-in. Widmer column, and the fraction boiling at 118-119°/15 mm. is collected. The yield of ethyl α-isovalerylisovalerate is 13.3 g. (63%).

Mixed Ester Condensation. Ethyl a-Ethoxalylisobutyrate.¹⁵ To a solution of 0.205 mole of triphenylmethylsodium in approximately 1400 cc. of ether, contained in a 2-l. Erlenmeyer flask, is added 27.3 cc. (23.8 g., 0.205 mole) of ethyl isobutyrate (b.p. 111–112°). The flask is stoppered, shaken, and allowed to stand. After five minutes, 27.8 cc. (30 g., 0.205 mole) of ethyl oxalate (b.p. 72–74°/10 mm.) is added slowly and with shaking. The reaction is vigorous, and the mixture may boil gently. After standing for ten minutes at room temperature, the reaction mixture is acidified with 15 cc. of glacial acetic acid and extracted with 100 cc. of water. The resulting ether solution is washed free from excess acid with 50-cc. portions of saturated sodium bicarbonate solution. The ether solution is dried by shaking with anhydrous sodium sulfate and

allowing to stand over Drierite. The solution is filtered and the other distilled on a water bath. The residue is distilled in vacuum, and the fraction boiling up to 200°/50 mm. is fractionated through a 6-in. Widmer column. The yield of ethyl a-ethoxalylisobutyrate (b.p. 122-

123/15 mm.) is 27.2 g. (61%).

EXAMPLES OF THE ACETOACETIC ESTER TYPE OF CONDENSATION

densations between different esters; in Table V, intramolecular cyclizations; in Table VI, intermolecular condensations and cyclizations; in

In Table 111 are listed self-condensations of esters; in Table IV, con-

Table VII, ester-acid chloride condensations.

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Pater	Condensing Agent	Product	Yield, %	Refer-
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f-llutyl neetato	Triphenylmethyleodium	(-Intyl neoloncotato	<u>2</u> :	Ξ.
t-Butyl newlate	Propropylnuguesium bromido	Clariyl neoloncolato	? ?	ន៍ន៍
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Phenyl newfate	Sodium phenoxide	Though acotoncounto	=	R 2
Benzyl neetato	Sodium benzyloxide	Benzyl neotoneolnto	Linco	57
Benayl acetato	Triphenylmethyleodium	Benzyl neotoneotato	- -	គ <i>ុ</i>
Benzhydryl acetato	Sodium benzhydrylato	Bonahydryl neetoneotato	Car.	= S
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⁴⁶ Higley, Am. Chem. J., 37, 299 (1907); Kuts and Adkma, Ferkin and Pratt, J. Chem. Soc. 95, 161 (1909). J. Am. Chem. Soc., 62, 4392 (1930).

Tethyl c,y-dimethoxyacetoacetate

** Ivanov and Spasov, Bull. soc. chim., [4] 49, 375 (1931).
** Fratt and Robinson, J. Chem. Soc., 127, 193 (1925).

CONDENSATIONS HETWERN DIFFERENT ESTERS

Rofer- enco	\$\$\$\$\$\$\$\$	43	09	61	62	62, 63, 64, 64, 64, 65, 67, 40, 68, 68, 68, 68, 70, 70, 70, 71, 66, 71
Yield, R	$\begin{array}{c} 11\\ 19-22\\ 18\\ 22\\ 9\\ 15-20 \end{array}$	7	40-18	1	22	14 16 90 90 90 90 90 70 70 10 10 80 85 61 61 85 61 61 85 61 61 85 61 85 85 85 85 85 85 85 85 85 85 85 85 85
Product	Ethyl propionylacetato Ethyl n-butyrylacetato Ethyl n-valerylacetato Ethyl n-valerylacetato Ethyl n-heptoylacetato Ethyl isovalerylacetato Ethyl isovalerylacetato	Ethyl 7,7-diethoxynectoncotato	Ethyl 7,7-diethoxyacetosuccinato	Ethyl formylacetate (sodium salt	Ethyl formylncetato (sodium salt	Ethyl ca-formylpropionato Ethyl ca-formylphonylnectato Ethyl formylphonylnectato Ethyl formylsuccinato Methyl formylsuccinato Ethyl r-formylsuccinato Ethyl r-formylsuccinato Ethyl r-formylsochato (crudo) Ethyl e-formylsochato (crudo) Ethyl e-formylsochato (sodium sult) Uothyl kethynto Ethyl ca-oxalyl-n-butyrato Ethyl ca-oxalyl-n-butyrato Ethyl ca-oxalyl-n-butyrato Ethyl oxalylphonylnectato Ethyl oxalylphonylnectato Ethyl oxalylphonylnectato Ethyl oxalylphonylnectato Ethyl ca-oxalyl-r-phenylnectato Ethyl ca-oxalyl-r-phenylnectato Ethyl oxalylphonylnectato Ethyl oxalylphonylnectato Ethyl oxalylphonylnectato Ethyl ca-oxalyl-r-phenyl-r-butyrato
Condensing Agent	Sodium Sodium Sodium Sodium Sodium Sodium	Sodium	Sodium	Sodium	Sotlium othoxido	Sodium ethoxido Trinheuylmethylsodium Sodium Sodium Sodium Sodium Potassium ethoxido Potassium ethoxido Potassium ethoxido Sodium or sodium othoxido Sodium or sodium othoxido Sodium ethoxido Sodium ethoxido Sodium ethoxido Sodium ethoxido Sodium ethoxido Tripheuylmethylsodium Sodium ethoxido Tripheuylmethylsodium Sodium othoxido Sodium othoxido Sodium othoxido
Ester Acylnted	Ethyl acetato Ethyl acetato Ethyl acetato Ethyl acetato Ethyl acetato Ethyl acetato	Ethyl acetato	Ethyl succinate	Ethyl acetato	Ethyl acetato	Ethyl propionato Ethyl isobutyrato Ethyl isobutyrato Ethyl succinato Ethyl succinato Kethyl succinato Ethyl crotonato Ethyl rectato Ethyl accate Ethyl accate Ethyl accate Ethyl accate Ethyl accate Ethyl accate Ethyl accate Ethyl henyionato Ethyl propionato Ethyl propionato Ethyl phenyincetato Ethyl phenylaccate Ethyl phenylaccate Ethyl phenylaccate Ethyl phenylaccate Ethyl phenylaccate Ethyl phenylaccate Ethyl phenylaccate Ethyl phenylaccate
Acyluting Ester	Ethyl propionate Ethyl n-butyrato Ethyl n-wherato Ethyl n-heptonto Ethyl isovalerato	benzonto Ethyl diethoxy-	acetato Ethyl diethoxy-	ncetato Ethyl formato	Ethyl formate	Ethyl formato Ethyl formato Ethyl formato Ethyl formato Methyl formato Ethyl formato Ethyl formato Ethyl ornato Ethyl oxalato

			O	ONDE	NSAT	IONS	BETWEEN	DIFFE	REAL PRIEM
23	74	7.5	92	44	78	80, 80a 47, 40,	6. 8. 8. 8. 8. 8. 8. 8. 8. 8. 8. 8. 8. 8.	711a 71a	, Soc., 16, 0 (note 3) 7., 22, 885 774 (1934).
40	22	8	8	55	59 1	28-37 55-70	24.838	1833	938). 2] 95, 27em, 2] 95, 27 2, 95, 27 2, 95, 27 2, 95, 16, 11 2, 950 (11
Ethyl 7-exalylerotonate (sedium	Ethyl y-oxalylerotonate (potassium	Methyl 7-oxalyl \theta-methylcrotonate	Chotassum salt) Ethyl coxalylsorbate (potassium	Ethyl oxalylsuccinate Ethyl oxal-dioxalylsuccinate (sodi-	um salt) Ethyl o-oxalylgluterate Ethyl o-oxalyl o'-methylglutarate	Ethyl benzoylacetate Ethyl benzoylacetate	Methyl benzoylacetste Elby a-bensoylacetste Elbyl a-bensoylachtyrste Elbyl benzoylamethylacetste Elbyl o-anisoylacetste	Ethyl prannsoylacetate Ethyl furopionylacetate Rehyl propionylacetate Ethyl propionylacetate	11 [Trieblorg and Paret Or p. Sprident, 14, 94 (1935). 12 (1900). 13 (1900). 13 (1900). 14 (1900). 15 (1900). 15 (1900). 15 (1900). 16 (1900). 17 (1900). 18 (1900).
Sodium or sodium ethoxide		Potsasium ethoxide	Potassum ethoxide	Sodium ethoxide Sodium ethoxide	Sodium ethoxide Sodium ethoxido	Sodium ethoxide Sodium	Sodium Sodium ethoxide Sodium ethoxide Trophenylmetbylsodium Sodium	Sodum Sodum Trphenylmethylsodium Trphenylmethylsodium	(1908); (19
Fthyl crotonate		Protonate		9.9	glutarate	Ethyl acetate Ethyl acetate	Methyl acetate Ethyl propionate Ethyl bechtyrate Ethyl socutyrate Ethyl socutyrate		** Bugeley and Johnson, J. Am. Chem. Shot, 41, 2909 (1923). **Producing, Prog. 107 (1952). **The Members, Prog. 107 (1952). **Wildrams, Prog. 107 (1952). **Wildrams, Prog. 107 (1952). **Wildrams, Prog. 207 (1952). **Wildrams, P
	Ethyl oxalate		Ethyl oxagica			Ethyl benzoate		Ethyl p-anisate Lthyl furcate Thenyl propionate p-Diphenyl propi- onate	in Hugeley and Jo in Pechanas, Ber in De Combs, Am in De Combs, Am in Whilenens, Ber in Whilenens, Ber in Whilenens, Jo in Whilenens, An in Whilenens, An in Whilenens, An in Whilenens, An in Whilenens, An in Whilenens, Re in Whilenens, Re in Whilenens, Re in Whilenens, Re in Whilenens, Re in Whilenens, Re in Whilenens, Re in Manamorking, An in Abamorolich Re in Abamoro

TABLES V

		THE REPORT OF THE PROPERTY OF
INTRANOLECULAR CONDENSATIONS (DUCKNARN REACTION)	Product	Sodium Sodium Sodium Sodium 2-Carboethoxyeyelopentanono 2-Carboethoxyyeyelopentanono 2-Carboethoxyyeyelopentanono Sodium 2-Carboethoxyyeyelopentanono Sodium Sodium Sodium Sodium Sodium Sodium Sodium Sodium Sodium Sodium Sodium Sodium Sodium Sodium Sodium 2-Carboethoxyeyeloheptanono 2-Carboethoxyeyeloheptanono 2-Carboethoxyeyeloheptanono 2-Carboethoxyeyeloheptanono 2-Carboethoxyeyeloheptanono 2-Carboethoxyeyeloheptanono 2-Carboethoxyeyeloheptanono 2-Carboethoxyeyeloheptanono 2-Ethyl 2,5-dienrboethoxyeyelopentanono non 2-Ethyl 2,5-dienrboethoxyeyelopentanono non 2-Carboethoxyeyelopentanono non 3-Dienrhylsalieylio acid 4,0-Dienrhylsalieylio acid 133, 1133 (1955).
MAN CONDENSATIONS (Condensing Agent	annido methoxido 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
Intranolise	Ester	Fiftyl armethyladipato Edyl ermethyladipato Edyl ermethyladipato Edyl gemelato Nerhyl evter of 1.5 methoxy-2-methyl 2-carboxy- Edyl gluarato Ethyl archyl-archyladipato Ethyl archyl-archyladipato Ethyl archyl-archyladipato Ethyl archyl-archyladipato Ethyl archyl-archyladipato Sodium ethyl archylachyladipato Methyl armethyl-archylachyladipato Methyl armethyl-archyladipato Methyl archyladipato Me

TABLE VI
INTERMOLECTEAN CONDENSATIONS AND CYCLICATIONS

Acylating Ester	Ester Aeylated	Condensing Agent	Product	Yield,	Yield, Refer-
Ethyl succinate	Ethyl succinate	Sodium ethoxide	Ethyl enter of evelopexanedions.		
Ethyl auconate n-Propyl suconate			1,4-dicarboxy lie acid-2,5 Ethyl ester of above acid	3 &:	51, 32
Allyl succenate Ethyl oxalate	Jeobutyl succinate Allyl succinate Ethyl glutarete	Sodium	Robuty 1 cater of above acid Allyleater of above acid	5 ₹ I	
Policy	D1111111111111111111111111111111111111	Soutum ethoxide (alc. soln.)	Soutum ethoxide (ale, sola) 3,5-Dieartsoethoxy eyelopentanedia	8	8
ANTONI OXABATE	S-Methylglutarate	Sodium ethoxide (alc. sola)	Sodium ethoxide (ale, soln.) 3,5-Dieartocthoxy-4-methylevela.	2	2
Ethyl oxalate	S-Phenylglutarate	Sodium ethoxide (ale. soln.)	Sodium ethoxide (ale. soin.) 3.5-Dicarboethoxy-4-plana) and	3	3 8
Methyl oxalate Ethyl oxalate	Methyl 2,3-dimethylglutarate Sodium methoxide Ethyl 5,3-dimethylglutarate Sodium ethoxide	Sodum methoxide Sodum ethoxide	pentanedione-1,2 Dimethyl diketospocamphorate	3 2	3 3
Ethyl phthalate	Ethyl acetate	ethoxide	2-Carboethoxy 1,3-diketohydrin-	I ow	54 (53)
Ethyl oxalate	Ethyl \$-ethoxycrotonate	Potassium ethoxide	dene Potamum enolate of 3-carboethoxy	8	3 %
			4-ethaxycyclopentene-3-dione-1,2 [(erude	(crude	3

** Lebermann, Ann., 404, 237 (1914).
** Welcomus and Schollkoph, J. Prakt. Chrm., [2] 95, 281 (1917).

LABLE VI

CONDENHATIONS HETWERN ESTELLS AND ACID CHLORIDES

11113 11	
Yield, Refer-	8, 15 15 15 15 15 15 15 15 15 15 15 15 15 1
Yiold,	51 55-74 55-74 50-65 75 75 75 75 75 75 76 76 76 76 76 76 76 76 76 76 76 76 76
Product	Ethyl c-ncotylisobutyrato Ethyl c-hutyrylisobutyrato Ethyl c-isobutyrylisobutyrato Ethyl c-banzoylisobutyrato Ethyl dimethylmulonato Diethyl dimethylmulonato Ethyl propionylmothylethylucotato Ethyl benzoylmothylethylucotato Ethyl penzoyldiethylucotata Ethyl propionyl acetato Ethyl dipropionyl acetato Ethyl dipropionylacetato Ethyl dipropionylacetato Ethyl dipropionylacetato Mothyl benzoyldiphenylacetato Mothyl benzoyldiphenylacetato Mothyl benzoyldiphenylacetato Mothyl benzoyldiphenylacetato O-Benzoyl G-carbomethoxyfluoreno O-Benzoyl G-carbomethoxyfluoreno
Condensing Agent	Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm Triphenylmethylsodinm
Ester	Acetyl chlorido Belaytytl chlorido Benzoyl chlorido Methyl diphenylacetato
Acid Chlorido	Acetyl eldorido Belbyl isobutyrata Belbyryl eldorido Belbyl isobutyrata Benzoyl eldorido Pethyl isobutyrata Benzoyl eldorido Benzoyl eldorido Benzoyl eldorido Benzoyl eldorido Benzoyl eldorido Benzoyl eldorido Benzoyl eldorido Benzoyl eldorido Acetyl eldorido Benzoyl eldorido Benzoyl eldorido Acetyl eldorido Benzoyl eldorido Benzoyl eldorido Acetyl eldorido Benzoyl eldorido

BRIEF SURVEY OF METHODS OF SYNTHESIS OF SIMPLE 6-KETOESTERS

In this section the more important methods of synthesis of various types of simple 8-ketoesters are briefly considered.

(A) CH2COCH2CO2C2H2 and CH2COCH2CO2R. For many years ethyl acetoacetate has been prepared in the laboratory and in industry by the self-condensation of ethyl acetate in the presence of sodium. Recently, diketene has become commercially available ** and is now used to prepare ethyl acetoacetate: the reaction may be represented as follows.

$$\begin{array}{c} CH_2 = C - CH_2 + C_2H_4OII \rightarrow CH_4COCH_5CO_2C_2H_6 \\ \downarrow \qquad \qquad \\ O - CO \end{array}$$

Acetoacetic esters of other alcohols have been prepared satisfactorily by the self-condensation of the appropriate ester (CH3CO2R), by the alcoholysis of ethyl acetoacetate, and by the reaction of diketene with the appropriate alcohol; "s the last method is probably the most convenient when diketene is available.

(B) CH₃COCHRCO₂C₂H₅. These β-ketoesters are commonly prepared by the alkylation of the sodium enolate of ethyl acetoacetate with the appropriate alkyl halide. Mixed ester condensations have not been satisfactory for the preparation of \$\beta\$-ketoesters of this type. Ethyl a-isopropylacetoacetate has been prepared in good yield (60-70%) by the alkylation of ethyl acetoacetate with isopropyl ether in the presence of horon trifluoride #7

CH₂COCH₂CO₂C₂H₄ + [(CH₃)₂CH]₂O
$$\xrightarrow{\text{BF}_3}$$
 CH₃COCHCO₂C₂H₄
 $\xrightarrow{\text{HC}(\text{CH}_3)_2}$

(C) CH₃COCR₂CO₂C₂H₅. These β-ketoesters are commonly prepared by the dialkylation of ethyl acetoacetate, that is, by the alkylation of compounds of type B. Ethyl a-acetylisobutyrate (in which R is methyl) has been prepared in good yield (51%) from the sodium enolate of ethyl isobutyrate and acetyl chloride. Methyl α,α-diphenylacetoacetate, CH₃COC(C₆H₅)₂CO₂CH₃, has been prepared in a similar manner.

(D) RCOCH2CO2C2H5 (in Which R is an Alkyl or Aryl Group Other Than Methyl). A number of methods have been used for the preparation of β -ketoesters of this type, but none appears to be an entirely satisfactory general method. The following have been used most frequently; (1) the acylation of ethyl acetate by other ethyl esters; (2) the acylation

¹¹ Boese, J. Ind. Eng. Chem., 32, 16 (1946).

¹⁷ Hauser and Breslow, J. Am. Chem. Soc., 62, 2392 (1940).

of acetonitrile by esters and subsequent alcoholysis of the ketonitrile; (3) the acylation of ethyl acetoacetate with acid chlorides or anhydrides and the subsequent ammonolysis or alcoholysis of the product; (4) the reaction of ethyl cyanoacetate with Grignard reagents; (5) the hydration of α,β -acetylenic acids and esterification; (6) the acylation of methyl ketones with ethyl carbonate; and (7) the oxidation of β -hydroxyesters (p. 11).

The acylation of ethyl acetate by another ester (method 1) consists in a mixed ester condensation, which, as already pointed out (p. 270), is in general satisfactory only when the acylating ester has no active hydrogen. The acylation of acetonitrile with esters (method 2) ^{69, 83} appears to have had a somewhat more limited use than method 1. The nitrile and ester are condensed by means of sodium ethoxide (or triphenylmethylsodium) ⁵⁹ and the resulting β -ketonitrile alcoholized. ⁵⁹⁻⁸³

$$RCO_2C_2H_5 + CH_3CN \rightarrow RCOCH_2CN \rightarrow RCOCH_2CO_2C_2H_5$$

Method 3 may be represented as follows.

$$\begin{array}{cccc} \text{CH}_2\text{COCH}_2\text{COC}_2\text{H}_5 & \xrightarrow{\text{RCOCI}} & \text{CH}_2\text{COCHCO}_2\text{C}_2\text{H}_5 & \xrightarrow{\text{NH}_2} & \text{RCOCH}_2\text{CO}_2\text{C}_2\text{H}_5 \\ & & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & \\ & & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & & \\ & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & & \\ & \\ & & \\ & & \\ & \\ & \\ & & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\$$

The acylation of ethyl acetoacetate (in the form of its sodium enolate) is readily carried out with acid chlorides or anhydrides, so and the ammonolysis (or alcoholysis) of the acyl acetoacetic ester at least in several cases gives good yields of the desired acyl acetate. However, ethyl propionylacetoacetate on ammonolysis gives a mixture of ethyl propionylacetate and ethyl acetoacetate which is difficult to separate. The acylaterate and ethyl acetoacetate which is difficult to separate.

Method 4 c. 2 may be represented as follows.

The Grignard reagent may react not only with the cyanide group, but also with the ester group and with the active hydrogens, resulting in mixtures of products. It has been shown that 1 mole of ethyl cyanoacetate is capable of reacting with 4 moles of Grignard reagent.⁵² It should be pointed out, however, that the β -ketoester is not contaminated with ethyl acetoacetate as sometimes happens with methods 1 and 3.

¹¹ Cox, Kroeker, and McElvain, J. Am. Chem. Soc., 55, 1172 (1934).

Abramovitch and Hauser, J. Am. Chem. Soc., 64, 2720 (1942).
 Bouveault and Bongert, Bull. soc. chim., [3] 27, 1045 (1902).

¹¹ Boureault and Bongert, Bull. soc. chim., [3] 27, 1089 (1902).

²² Blaise, Compt. rend., 132, 978 (1991).

⁵³ Brekpot, Bull. voc. chim. Belg., 32, 386 (1923).

Method 5 *4 may be represented as follows.

In general, the hydration of the acetylenic acids appears to give good yields of β-ketoacids, but the esterification of the latter may be difficult. The use of the method is somewhat limited by the fact that the acetylenic acids or hydrocarbons are generally not readily available.

Method 6 s may be represented as follows.

This method consists in heating or digesting the ketone with sodium or potassium ethoxide (or other alkoxide) in a large excess of ethyl carbonate (or other alkyl carbonate). This direct method appears to be very satisfactory for the synthesis of several of the higher acylacetates, but it is not satisfactory for the synthesis of ethyl propionylacetate or cthyl isobutyrylacetate. 95

In Table VIII are collected the yields that have been reported in the preparation of typical \$-ketoesters by these methods. The question

TABLE VIII PERCENTAGE YIELDS OF ETHTL ACYLACETATES RCOCH: CO2C1H5 BT VARIOUS METRODS

Acyl Group (RCG)	Method	Method 2	Method 3	Method 4	Method 5	Method 6
CH ₂ CH ₂ CO-	11	3319	10-12 75 °	10-60 40	÷	?
CH ₄ (CH ₂) ₂ CO— (CH ₃) ₂ CHCO—	19-22	36	"	_	-	Poor
CH ₃ (CH ₂) ₃ CO— (CH ₃) ₂ CHCH ₂ CO—	"Poor"	_	"Excellent"	15	_	60
CH4(CH4)4CO-	22		"Excellent"	=	50-50	65 74 *
CH ₂ (CH ₂) ₅ CO— CH ₂ (CH ₂) ₅ CO—	- 1	_	~	-	76	_
C ₆ H ₅ CO	55-70 d	42	49~58 *	-	(erude)	60

a Yielda given are for the methyl acylacetates

⁵ Over-all yield for both acylation and ammonolysis

⁶ Yield for n-propyl acylacetate

d With sodium ethoxide as condensing agent the yield is 37% so

Moureu and De Lange, Bull. soc churt , [3] 29, 666 (1903).

Mallingford, Homeyer, and Jones, J. Am. Chem. Soc., 63, 2252 (1941).

mark indicates that the method was used but that no yield was reported. It should be noted that the yields given under method 3, with the exception of cthyl benzoylacetate, are for the ammonolysis reaction only and do not include the yields obtained in the preparation of the acyl acetoacetic esters. The yields given under method 1 are those obtained under "special conditions" with sodium as condensing agent and are calculated without taking into consideration the quantities of starting materials recovered unchanged.

It can be seen from Table VIII that only one of the β -ketoesters listed, ethyl (methyl, in method 3) n-butyrylacetate, has been prepared by at least five of the methods. This compound appears to be best prepared by method 3; however, the 75% yield does not include the acylation of ethyl acetoacetate. Ethyl isobutyrylacetate has been prepared in fairly good yield 88 by method 2, while several of the higher aliphatic β -ketoesters have been prepared satisfactorily by methods 3, 91 5, 94 or 6.95 Ethyl benzoylacetate has been prepared satisfactorily by methods 1,47 2,80 3,96 and 6,95 the Organic Syntheses method 96 being basically the same as 3, and the commercial method 40 basically the same as 1.

None of the methods described above appear to be satisfactory for the preparation of ethyl propionylacetate. One investigator reported a vield of 55% 62 using method 4, but another obtained only a 10-12% yield 93 by this method. Although Fischer and Orth 97 record a yield of 60% by method 4, they point out that the preparation is inferior to method 3, in which the yield is only 10-12%. Ethyl propionylacetate has been obtained in fair yield (44%) by condensing the sodium enolate of ethyl acetate (prepared by means of triphenylmethylsodium) with v-diphenyl propionate. na similar manner, n-amyl propionylacetate has been obtained from the sodium enolate of n-amyl acetate and phenyl propionate.714 In both cases essentially pure products were obtained; apparently the only disadvantage of the method is that a relatively large amount of triphenylmethylsodium is required. Ethyl propionylacetate has been prepared also from the sodium enolate of ethyl acetate and a large excess of propionyl chloride, but the yield was only 15%, the main product (39% yield) being the dipropionylacetate. 15 The latter on ammonolysis according to the second step of method 3 gave ethyl propionylacetate in a yield of 50%.15

(E) RCOCHRCO₂C₂H₅. 1. Special Case: RCH₂COCHRCO₂C₂H₅, in Which the Two Groups, R, Are the Same. Most β-ketoesters of this kind are best prepared by the self-condensation of esters of the type RCH₂CO₂C₂H₅ or by the action of ethanol on the appropriate diketene.

⁹⁶ Shriner, Schmidt, and Roll, Org. Syntheses, 18, 33 (1938).

⁹⁷ Fischer and Orth, "Die Chemie des Pyrolles," Vol. I, p. 404 (1934), Leipzig.

The acylation of ketones with ethyl carbonate is also satisfactory in certain cases 95

2. General Case: RCOCHRCO2C2H5 (the Two Groups, R. May Be the Same or Different). The only general method for the preparation of β-ketoesters of this type consists in the alkylation of unsubstituted β-ketoesters of type D. RCOCH, CO₂C, Hs. When prepared by method 6 described above, the latter are obtained in the reaction mixture in the form of their sodium enolates and may be alkylated directly. Similarly, the cleavage of acyl acetoacctic esters by means of sodium ethoxide gives the sodium enolates of B-ketoesters of type D, which may be alkylated directly.23

 $\text{CH}_{2}\text{COCHCO}_{2}\text{C}_{2}\text{H}_{8}\xrightarrow{\text{NaOC}_{8}\text{H}_{4}}\text{RCOCH}_{8}\text{CO}_{2}\text{C}_{7}\text{H}_{8}\xrightarrow{\text{RX}}\text{RCOCHRCO}_{2}\text{C}_{2}\text{H}_{8}$ BCO

With primary alkyl halides over-all yields of 61-75% are reported.10 β-Ketoesters of the type CoHsCOCHRCO2C2H3 may be prepared either by the alkylation of the unsubstituted compound," CoH3COCH2CO2C2Hs. or by the condensation of ethyl benzoate with propionitrile or higher aliphatic nitriles, followed by the alcoholysis of the resulting β -ketonitrile.* The latter method has given over-all yields of 37-42% in several different cases. **

 $C_tH_4CO_tC_2H_5 + RCH_4CN \xrightarrow{N_6OC_tH_4} C_tH_4COCHRCN \xrightarrow{C_tH_4OH}$ RCOCHRCO.C.II.

Ethyl a-benzoylpropionate has been prepared in 37% yield by the acylation of propiophenone with ethyl carbonate.*5

(F) RCOCR₂CO₂C₂H₅. 1. Special Case: R₂CHCOCR₂CO₂C₂H₅. in Which the Four Groups Are the Same. One β-ketoester of this type, namely, ethyl sobutyrylisobutyrate, has been prepared in good yield by the self-condensation of ethyl isobutyrate, and it is possible that others might be prepared in a similar manner. But this β -ketoester is better prepared from the sodium enolate of ethyl isobutyrate and isobutyryl chloride.15

2. General Case: RCOCR2CO2C2H5, in Which the Three Groups, R, Moy Be the Same or Different. Certain β-ketoesters of this type have been prepared by the alkylation of compounds of type E or by the dialkylation of acylacetates (compounds of type D); " obviously, the complete synthesis requires several steps and at least in certain cases it is unsatisfactory. A more direct and better method for the synthesis of

^{*} Bouveault and Locquin, Bull. soc. chim., [3] 21, 588 (1904).

See, for example, Hope and Perkin, J. Chem. Sec., 95, 2012 (1909).

compounds of the type $RCOCR_2CO_2C_2H_5$ consists in condensing the appropriate ester, in the form of its sodium enolate, with a suitable acid chloride.¹⁵ The yields are high (50-75%), and the products are of high purity.

(G) Miscellaneous β -Ketoesters. Ethyl ethoxalylacetate and ethyl formylacetate and their homologs are probably best prepared by mixed ester condensations (see p. 271). Also a number of cyclic β -ketoesters are probably best prepared by ester-ester condensations (see pp. 274, 275).

CHAPTER 10

THE MANNICH REACTION

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INTRODUCTION

The Mannich reaction consists in the condensation of ammonia or a primary or secondary amine, usually as the hydrochloride, with formal-dehyde and a compound containing at least one hydrogen atom of pronounced reactivity. The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl or substituted aminomethyl group. The product from acetophenone, formal-dehyde, and a secondary amine salt is an example. In the equation the reactive hydrogen atoms are underlined.

$$C_{e}H_{\sharp}COC\underline{H}_{2}+CH_{2}O+R_{2}NH\cdot HCl\rightarrow C_{e}H_{\sharp}COC\underline{H}_{2}CH_{2}NR_{2}\cdot HCl+H_{2}O$$

The product from a methyl ketone contains reactive hydrogen atoms, and in some cases it is possible to carry the reaction one step further, yielding a compound with two basic groups.

$$C_6H_2COC\underline{H}_2NR_2\cdot HCl + CH_2O + R_2NH\cdot HCl \rightarrow$$

$$C_tH_sCOCH(CH_sNR_s\cdot HCl)_s + H_sO$$

If the substance used in the condensation contains reactive hydrogen atoms on two or more different carbon atoms, then substituted aminomethyl groups may appear at different points in the molecule, leading to a mixture of isomers. If the condensation is effected with a primary amine or its salt, the product is a secondary amine.

 $\mathrm{C_{2}H_{4}COCH_{2}+CH_{2}O+RNH_{2}\cdot HCl} \rightarrow \mathrm{C_{4}H_{4}COCH_{2}CH_{2}NHR\cdot HCl+H_{2}O}$

In many cases the resulting secondary amine reacts further to yield a tertiary amine.

C₂H₄COCH₂ + CH₂O + C₄H₄COCH₂CH₂NHR·HCl →

(C4H4COCH2CH2)2NR-HCI+H2O

Frequently such products, derived from two molecules of ketone, two molecules of formaldehyde, and one molecule of primary amine, are unstable and readily undergo cycluzation. The compounds obtained from acetone, formaldehyde, and methylamine are illustrative.

The product to be expected from a Mannich reaction involving an ammonium salt is a primary amine. In many cases, the primary amine so produced reacts further, as above, to form a secondary amine, a tertiary amine, or a cyclic substance. The situation is further complicated by the fact that methylamine, produced from the ammonium salt and formaldehyde, also takes part in the reaction. For example, the compounds shown above as products of acetone, formaldehyde, and

¹(a) Mannich and Ball, Arch. Pharm., 284, 63 (1920); (b) Mannich and Ritsert, Sul., 284, 164 (1936).

methylamine hydrochloride are also obtained from acetone, formaldehyde, and ammonium chloride. 16. 2a

The first observation of a condensation of the type now known as the Mannich reaction was made by Tollens, who isolated the tertiary amine from ammonium chloride, formaldehyde, and acetophenone. Later Petrenko-Kritschenko and his students studied condensations of this kind but failed to recognize the reaction as a general one. The detailed study by Mannich, begun in 1917, was initiated by the observation that antipyrine salicylate, formaldehyde, and ammonium chloride reacted to form a tertiary amine.

$$\begin{array}{c} CH_1 \\ N - CCH_2 \\ 3C_tH_1N_1 \\ 5 - 4 \\ C - CH \\ O \\ Antipyrine \end{array} + 3CH_2O + NH_4Cl \rightarrow \begin{bmatrix} CH_2 \\ N - CCH_2 \\ C_tH_5N \\ C - C - CH_2 - \\ N - HCl \\ O \\ Antipyrine \end{array}$$

Since Aminopyrine (Pyramidon, 4-dimethylaminoantipyrine) failed to react, it was evident that the reaction involved the hydrogen atom of carbon 4 of antipyrine.

The mechanism of the Mannich reaction has not been established. The addition of the amine to formaldehyde has been considered as a possible primary step.^{5a,b}

The fact that, in the case of antipyrine, the reaction of dimethylaminomethanol gives a poorer yield of condensation product than either formaldehyde and the amine or formaldehyde and the amine hydrochloride indicates that this view is not correct. The possibility that the initial step is the formation of the methylol from the ketone has been examined.

²² See also Jacobson, J. Am. Chem. Soc., 67, 1999 (1945).

²⁵ van Marle and Tollens, Ber., 36, 1351 (1903).

² Schäfer and Tollens, Ber., 39, 2181 (1906).

⁴ Petrenko-Kritschenko and co-workers: (a) Ber., 39, 1358 (1906); (b) Ber., 41, 1692 (1908); (c) Ber., 42, 2020 (1909); (d) Ber., 42, 3683 (1909).

⁵ Mannich and Krösche, Arch. Pharm., 250, 647 (1912).

⁵⁴ See Bruson and Butler, J. Am. Chem. Soc., 68, 2348 (1946).

⁵⁵ Note the interaction of dialkylaminomethanols with nitroparaffins. See for references, Zief and Mason, J. Org. Chem., 8, 1 (1943).

⁶ Bodendorf and Koralewski, Arch. Pharm., 271, 101 (1933).

The methylols of acetone and cyclohexanone do condense with dimethylamine to give the expected products. However, the methylol from antipyrine does not react at all with dimethylamine. Apparently neither of these processes represents the primary step of the Mannich reaction

THE SCOPE OF THE MANNICH REACTION

The Use of Secondary Amines

The secondary amines which have been used successfully are listed in Table f

TABLE I SECONDARY AMINES IN THE MANNICE REACTION

Dimethylamine Piperidane

Diethylamine

1,2,3,4-Tetrahydrossoquinoline 6-Methoxy-1,2,3.4-tetrahy drossoquinoline Diethanolamine

Morpholine Dipropylamine

Piperazupe Di-n-butylamine .Methylaminopropiophenone Diisoamylamine e-Acetylethylbenzylamine Dibenzy lamine

Benzyl-(2-cyclohevanonylmethyl)-amine Methyldiethylethylenedismine 3.4-Methylenediovybenzyl-(2-cyclohevanonyl-Methylaniline methyl)-amine

Dimethylamine is very reactive and usually leads to excellent yields. Diethylamine appears to be less reactive; it has been reported that the typical condensation does not take place with ethyl methyl ketone, diethylamine, and formaldehyde. On the other hand, formaldehyde and this amine do give normal products with acetone, benzalacetone, acetophenone, and several derivatives of the last. 11. 12. It has been reported that 2-acety liuran and formaldehyde react normally with salts of dimethylamine, dipropylamine, di-n-butylamine, and diethanolamine, but not with the salt of diethylamine.13 In other cases where dimethylamine, diethylamine, and dipropylamine have given good results, di-n-butylamine and diethanolamine have failed to react." The cyclic secondary amines mentioned above generally react about as well as dimethylamine. However, dicyclohexylamine 14 and tetrahydroquinoline 11. 15 are said not to take part in the reaction.

- ⁷ Kermack and Musr. J. Chem. Soc., 3089 (1931). du Feu, McQuillin, and Robinson, J. Chem. Soc., 53 (1937).
- Mannich and Schütz, Arch. Pharm., 255, 684 (1927).
- 19 Blocke and Burckbalter, J. Am. Chem. Soc., 54, 451 (1942). 11 Mannich and Lammering, Ber., \$5, 3510 (1992).
- 11 Mannich and Dannehl, Arch. Pharst . 276, 206 (1935). 12 Levvy and Nisbet, J. Chem. Soc., 1053 (1938).
- 14 Burger and Bryant, J Am. Chem. Soc , 53, 1054 (1941). 14 Burger and Mosettig, J. Am. Chem. Soc., 53, 1570 (1936).

With Ketones. Saturated ketones, cycloalkanones, $\alpha.6$ -unsaturated ketones, aliphatic aromatic ketones, including those in which the aromatic ring is heterocyclic, and certain heterocyclic ketones containing a carbonyl group in the ring all undergo the Mannich reaction with secondary amines, usually in good yields.

In Table II are listed ketones which have been treated with formal-dehyde and salts of secondary amines with the successful formation of a β -dialkylaminoketone. In the formulas the replaceable hydrogen atom is underlined. A detailed list of the Mannich reactions involving these ketones is given in Table V, p. 331.

TABLE II
KETONES IN THE MANNICH REACTION

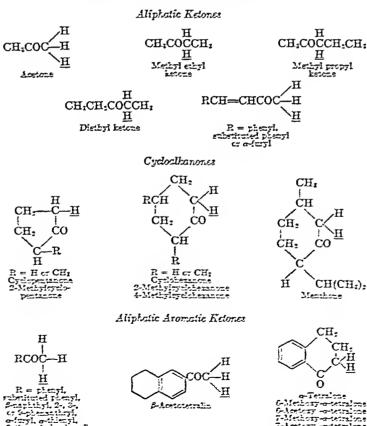


TABLE II-Continued

KETONES IN THE MANNICH REACTION-Continued

Alinhatic Aromatic Ketones-Continued

The following ketones have proved to be unreactive: o-aminoacetophenone and its acetyl and benzoyl derivatives; is m-aminoacetophenone (the acetyl and benzovl derivatives do react in this case 12); p-acetoaminoncetophenone; II and \$-tetralone.10 1-Phenyl-3-methylpyrazolone-5,17 1-phenyl-5-methylpyrazolone-3,17 and barbituric acid 17 do not react.

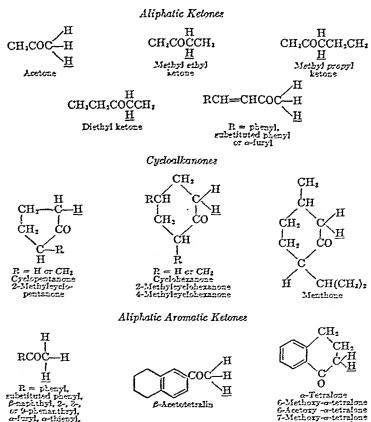
With Aldehydes. The behavior of aldehydes in the Mannich reaction is similar to that of ketones. The a-hydrogen atom of the aldehyde is substituted by a dialkylaminomethyl group. A secondary reaction which sometimes occurs involves the simultaneous introduction of a methylol group on the a-carbon atom.18

- 14 Mosettig and May, J. Org. Chem., 5, 528 (1940).
- 17 Mannich and Kather, Arch. Pharm., 257, 18 (1919).
- 18 Mannich, Lesser, and Silten, Ber., 65, 378 (1932).

With Ketones. Saturated ketones, cycloalkanones, α,β -unsaturated ketones, aliphatic aromatic ketones, including those in which the aromatic ring is heterocyclic, and certain heterocyclic ketones containing a carbonyl group in the ring all undergo the Mannich reaction with secondary amines, usually in good yields.

In Table II are listed ketones which have been treated with formal-dehyde and salts of secondary amines with the successful formation of a β -dialkylaminoketone. In the formulas the replaceable hydrogen atom is underlined. A detailed list of the Mannich reactions involving these ketones is given in Table V, p. 331.

TABLE II
KETONES IN THE MANNICH REACTION



-Acetory -a-tetralone

Chromasons

TABLE II-Continued

KETONES IN THE MANNICH REACTION-Continued

Aliphotic Aromatic Kelones -- Conlinued

The following ketones have proved to be unreactive: o-aminoacetophenone and its acetyl and benzoyl derivatives; "m-aminoacetophenone (the acetyl and benzoyl derivatives do react in this case "i); p-acetoaninoacetophenone; " and \$f\$-tetralone." 1-Phenyl-3-methylpyrazolone-5, " 1-phenyl-5-methylpyrazolone-3," and barbituric acid " do not react.

1-antipype4

With Aldehydes. The behavior of aldehydes in the Mannich reaction is similar to that of ketones. The a-hydrogen atom of the aldehyde is substituted by a dialkylaminomethyl group. A secondary reaction which sometimes occurs involves the simultaneous introduction of a methylol group on the a-carbon atom.

Antipyrine

¹⁶ Mosettig and May. J. Org. Chem., 5, 528 (1940).

Mosettig and May, J. Org. Cast., v. 357, 18 (1919).
 Mannich and Kather. Arch. Phorms., 257, 18 (1919).

Mannich and Kather, Area, Faire, 55, 378 (1933).

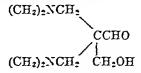
$$(CH_2)_2CHCH_2CHO + (CH_2)_2NH \cdot HCI + CH_2O \rightarrow CH_2OH$$

$$(CH_2)_2CHCHCHO + (CH_2)_2CHCCHO$$

$$(CH_2)_2CHCHCHO + (CH_2)_2CHCCHO$$

$$(CH_2)_2CHCHCHO + (CH_2)_2CHCCHO$$

In the case of acetaldehyde the only product isolated is one of more complicated nature in which two dimethylaminomethyl groups and one methylol group have entered the molecule.¹⁵



The aldehydes have been less extensively studied than the ketones and there are recorded merely the condensations of acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, isovaleraldehyde, and hexahydrobenzaldehyde with dimethylamine or piperidine hydrochloride. The products from the reactions are shown in Table V, p. 331.

With Acids and Esters. A number of acids containing highly active hydrogen atoms in the α -position can be used instead of aldehydes or ketones. When an acid is employed the free secondary amine, rather than its salt, is used. The acids which have given satisfactory results are listed in Table III. The replaceable hydrogen atoms are underlined.

TABLE III

ACIDS IN THE MANNICH REACTION

CXCH*CO*H	CH;COCH(R)CO;H
F-NO-C-H-CH-CO-H	$CH_2(CO_2H)_2$
C:H:COCH-CO-H	RCH(CO2H)2
6-X0 ⁻ C ⁻ H ⁻ CH(OH)СО-Н	RCH(CO2R)CO2H
CH₂COCO₂H	C ₂ H ₂ COCH ₂ CH(CO ₂ H) ₂
CH ₂ COC <u>H</u> 2CO2H	HO ₂ CCH ₂ CH(CO ₂ H) ₂

The replacement of a lone active hydrogen atom is illustrated by the reaction of ethylmalonic acid, formaldehyde, and dimethylamine.¹²

A side reaction which often occurs involves the decarboxylation of ¹³ Mannich and Ganz, Ber., 55, 3455 (1922).

the acid, as in the condensation of ethylacetoacetic acid with formal-dehyde and dimethylamine 20

$$\begin{array}{c} \text{CO}_{2}\text{H} \\ \text{CH}_{2}\text{CH}_{1}\text{CH} \\ \text{COCH}_{1} \end{array} + \text{CH}_{2}\text{O} + (\text{CH}_{2})_{2}\text{NH} \rightarrow \\ \text{COCH}_{2} \end{array}$$

CH₂CH₂CHCH₂N(CH₂)₂ + CO₂ + H₂O

In those cases where two dialkylamino groups enter the molecule, carbon dioxide is invariably eliminated.

With Phenols. The and p-hydrogens in phenols are sufficiently active to enter into the Mannich reaction. Thus, products from phenol, iii. a. 1-actentinophenol, ii. 2 and p-cresol, iii. methylphenol, ii. 2 and 4-methyrphenol, iii. 2-methyl-1-thylphenol, ii. 2 and 4-methyrphenol, iii. 2-methyl-1-thylphenol, iii. 2 and 4-methyrphenol, iii. 2-methylamine or piperidine or morpholine, have been reported. From p-cresol a mono- and a di-substitution product are obtained, and from phenol and m-cresol, trisubstitution products

$$\begin{array}{c} \text{OH} \\ \text{CH}_1\text{N(CH}_1)_2 \\ \text{CH}_2 \\ \text{CH}_3 \\ \text{CH}_3 \\ \text{CH}_3 \\ \text{NCH}_4 \\ \text{CH}_3 \\ \text{CH}_5$$

Interaction of 2-methyl-6-ethylphenol, formaldehyde, and dimethylamine is reported to yield a mixture of methylenedi-(2-methyl-6-ethylphenol) and 1-(dimethylaminomethoxy)-2-methyl-6-ethylbenzene."

With Acetylenes. Phenylacetylene and certain substituted phenylacetylenes, such as the 2-nitro, 2-amino, and 4-methoxy derivatives react readily with formaldehyde and secondary ammes.¹⁴

$$C_4H_4C \equiv CH + CH_2O + (C_2H_4)_2NH \rightarrow C_4H_4C \equiv CCH_2N(C_2H_4)_2$$

¹⁰ Mannich and Bauroth, Ber., 57, 1168 (1924).

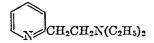
n Ger. pat., 92,309; FrdL, 4, 103 (1899).

Décombe, Compt. rend., 196, 866 (1933).
 Bruson and MacMullen, J. Am Chem. Soc., 63, 270 (1941).

Bruson and MacMusien, J. Am. Chem. Soc., 61, 765 (1939).
 Caldwell and Thompson, J. Am. Chem. Soc., 61, 765 (1939).

Décombe, Compt. rend., 197, 258 (1933).
 Mannich and Chang, Ber., 66, 418 (1933).

With α -Picolines and Quinaldines. Since an α -methyl group in a pyridine or quinoline nucleus has hydrogens of about the same activity as those in the methyl group of a methyl ketone, the Mannich reaction might be expected to take place with such molecules. α -Picoline, ²⁷ 2-methylquinoline ^{7, 27, 25} (quinaldine), 2-methyl-4-hydroxyquinoline, ²⁸ 2-methyl-8-nitroquinoline, ²⁸ and 2-ethoxy-4-methylquinoline ²⁸ have been condensed with dimethylamine, diethylamine, methyldiethylenediamine, piperidine, and methylaniline, either as the free amine or as the amine hydrochloride. Thus, α -picoline, formaldehyde, and diethylamine yield 2-(β -diethylaminoethyl)-pyridine. ²⁷



The Use of Primary Amines

The primary amines listed in Table IV have been used successfully in the Mannich condensation.

TABLE IV

PRIMARY AMINES IN THE MANNICH REACTION

Methylamine
Ethylamine
β-Hydroxyethylamine
β-Chloroethylamine
Allylamine
Benzylamine

β-Phenylethylamine
Ethylenediamine
Ethyl aminoacetate

ω-Aminoacetophenone
Tetrahydro-β-naphthylamine
Aniline *

3, 4-Methylene-dioxybenzylamine Hydrazine ¹⁷ and guanidine, ¹⁷ have failed to react.

* Reacts only in certain instances.

With Ketones. When a primary amine or its salt is used in a Mannich reaction the first product is a secondary amine, but this often reacts with more of the reagents to give a tertiary amine. Aliphatic ketones and primary amines give rise to a number of products; for example, four substances have been isolated from the reaction of formaldehyde, diethylketone, and methylamine hydrochloride.²⁹ The structures of some of them are still in doubt (see also the reaction of acetone, methylamine, and formaldehyde, p. 305).

²⁷ Tseou Héou-Féo, Compt. rend., 192, 1242 (1931).

²³ Ger. pat., 497,907; Frdl., 16, 2669 (1931).

²³ Mannich, Arch. Pharm., 255, 261 (1917).

With Aldehydes. Apparently the only known reaction involving an aldehyde, a primary amine, and formaldehyde is that of isobutyraldehyde and methylamine.²³

$$(CH_1)_2CHCHO + CH_2O + CH_2NH_2 \rightarrow (CH_2)_2CCHO$$
 CH_2NHCH_3

With Acids and Esters. The Mannich reaction of primary amines with acids containing active hydrogen atoms leads to the same types of compounds as described above in connection with secondary amines. As might be expected, the first product often undergoes further condensation to form a tertiary amine. The reaction of methylmalonic acid, formaldehyde, and methylamue is an example.⁷¹

$$CO_3H$$
 $2CH_3CH + 2CH_2O + CH_2NH_3 \rightarrow \begin{pmatrix} CO_2H \\ CH_3C - CH_3 \end{pmatrix} NCH_3$
 CO_3H
 CO_3H

When a primary amine is used with a polycarbonyl compound which contains reactive hydrogen atoms on carbon atoms located in the 1,3-positions with respect to each other, then cyclic products may be expected. Thus, esters of α,α-disthylacetonedicarbocylic acid react with formaldehyde and methylamine to give pyridones.³

If the pyridone contains hydrogen atoms on the 3- and 5-carbon atoms, the condensation may be carried one step further and a bicyclic system may be produced. For example, the pyridone obtained by a reaction of the Mannich type from methyl acctonedicarboxylate, acctaldehyde, and methylamine can be condensed with formaldehyde and methylamine.³²

Mannich and Woder, Ber., 65, 3\S (1932).
 Mannich and Kather, Ber., 53, 1368 (1920).

a Mannich and Schumann, Ber., 63, 2299 (1936)

¹² Mannich and Viet, Ber., \$3, 506 (1935).

The name "bispidin" has been suggested for the bicyclic ring system produced in such reactions. 3. 24

This reaction can be used to build up tricyclic systems. Thus, the hydrochloride of methyl tropanone-2,4-dicarboxylate reacts in the same way as the pyridone above.

A similar reaction occurs when a tetrahydropyrone ¹⁵ derivative is used in place of the pyridone. For example, a bicyclic product is obtained from ethyl dimethyltetrahydropyronedicarboxylate, formal-dehyde, and methylamine.

It has been suggested that the bicyclic ring system so formed be termed the "pydin" nucleus.

With Phenols and Acetylenes. No Mannich reactions involving primary amines and either phenols or acetylenes have been reported.

With a-Picolines and Quinaldines. Of the compounds containing a methyl group in the 2-position of a pyridine nucleus only 2-methyl-Snitroquinoline has been treated with a primary amine and formalde-

[&]quot; Mannish and Mohs, Ber., 63, 608 (1980);.

²⁵ Mannich and Mück, Ber., 63, 604 (1990).

hyde. The amine used was ethylamine, and the product was a tertiary amine 25

$$\bigcup_{\mathrm{NO}_{2}} \bigcup_{\mathrm{CH}_{3}} + \mathrm{CH}_{4}\mathrm{O} + \mathrm{C}_{1}\mathrm{H}_{1}\mathrm{NH}_{1} \cdot \mathrm{HCl} \rightarrow$$

$$\bigcup_{\mathrm{NO}_{2}} \bigcup_{\mathrm{NC}_{1}\mathrm{H}_{2}\mathrm{CH}_{3}} \mathrm{CH}_{4}\mathrm{CH}_{5} \Big)_{2}\mathrm{NC}_{2}\mathrm{H}_{1} \cdot \mathrm{HCl}$$

The Use of Ammonia

With Ketones. A primary amine is the first product to be expected from a Mannich reaction in which ammonia or an ammonium salt and formaldehyde react with a compound containing an active hydrogen atom. With the simple ketones subsequent reaction of the primary amine so formed usually leads to the production of tertiary amines. Salts of certain of these primary and secondary amines have been isolated and found to be stable, but the free bases change to the tertiary amines. The disproportionation of the primary and secondary amines obtained from aectophenone, formaldehyde, and ammonia is an example.88

$$3C_6H_4COCH_2CH_2NH_2 \rightarrow (C_6H_6COCH_2CH_6)_6N + 2NH_6$$

 $3(C_6H_6COCH_2CH_2)_2NH \rightarrow 2(C_6H_6COCH_2CH_6)_6N + NH_6$

In some instances cyclic products are obtained from ketones, ammonia, and formaldehyde. From acetophenone, ammonium chloride, and formaldehyde there has been isolated a substance which is believed to be a substituted piperidine." It readily changes to the salt of tri-(β-benzovlethyl)-amine.3

$$C_4H_4COCH$$
 C_4H_4COCH
 CH_4
 CH_5
 CH_5
 CH_5
 $CH_5CH_5COC_5H_6$
 $CH_5CH_5COC_5H_6$

44 Mannich and Alxhillah, Ber., 65, 113 (1935)

With cyclohexanone the tertiary amine is obtained directly,⁵ in analogy with the reaction of antipyrine ^{5, 37} (p. 306).

The formation of cyclic products derived from methylamine, by reaction of acetone, formaldehyde, and ammonium chloride, has been mentioned (p. 305). The reaction with diethyl ketone takes a similar course, producing a trimethylpiperidone.²⁹ Presumably, methylamine is first formed from ammonium chloride and formaldehyde.

With Acids. From the reaction of benzylmalonic acid, ammonia, and formaldehyde both a primary amine and a secondary amine have been isolated.¹⁹

In the case of phenylmalonic acid a primary amine is produced and decarboxylation occurs when ammonia is used.¹⁹

$$CO_2H$$
 $C_6H_5CH \rightarrow C_6H_5CH$ — CH_2NH_2
 CO_2H
 CO_2H

When ammonium chloride is employed the decarboxylated secondary amine is obtained.¹⁹

$$CO_2H$$
 $C_6H_5CH \rightarrow (C_6H_5CHCH_2)_2NH$
 CO_2H
 CO_2H
 CO_2H

RELATED REACTIONS

Aldehydes other than formaldehyde may be used in certain condensations of the Mannich type. Those which have been studied are acetaldehyde, phenylacetaldehyde, benzaldehyde, and anisaldehyde. These have been employed successfully with acetone, cyclohexanone, and esters of acetonedicarboxylic acid. The reactions appear to be limited to ammonia and primary amines and their salts. With acetone, aniline, and benzaldehyde a piperidone is obtained.^{4d}

²⁷ Mannich and Braun, Ber., 53, 1874 (1920).

An open-chain product is formed from cyclohexanone, phenylacetaldehyde, and benzylamine.28

Substituted piperidones are always produced when esters of acetonedicarboxylic acid are employed, as in the reaction of the methyl ester with allylamine and benzaldehyde "

Similar piperidones have been obtained by substituting for allylamine the following: ammonia, to methylamine, to ethylamine, to and β-hydroxyethylamine; " by employing acetaldehyde, instead of benzaldehyde, with ammonium bromide," methylamine," benzylamine," and β-phenylethylamine; " and by using allylamine, anisaldehyde, and methyl acetonedicarboxylate.34

⁴ Otto Hieronimus, Dissertation, Reshn, 1908.

³¹ Peter Peckelboff, Dissertation, Stuttgart, 1933. Ger pal., 510,184.

THE APPLICATION OF THE MANNICH REACTION IN SYNTHESIS

Unsaturated Compounds

Preparation of Ethylenic Compounds. The most characteristic property of many of the products obtained in the Mannich reaction, especially those derived from secondary amines, is the decomposition into the amine and an unsaturated compound. The various condensation products exhibit widely different stabilities. Some can be distilled under diminished pressure, 40 but most of them undergo decomposition when heated or subjected to steam distillation.

$$C_6H_5COCH_2CH_2N(CH_3)_2 \cdot HCl \rightarrow C_6H_5COCH = CH_2 + (CH_3)_2NH \cdot HCl$$

$$(Ref. 41)$$

$$(C_6H_5COCH_2CH_2)_2NCH_3 \cdot HCl \rightarrow C_6H_5COCH = CH_2 + C_6H_5COCH_2CH_2NHCH_3 \cdot HCl \quad (Ref. 41)$$

$$C_6H_5COCH_2CH_2NHCH_3 \cdot HCl \quad (Ref. 41)$$

$$CH_2NC_5H_{10} \cdot HCl \rightarrow CH_3CHCHO + (CH_3)_2NH \cdot HCl \quad (Ref. 42)$$

$$CH_3CHCHO \rightarrow CH_3CCHO + (CH_3)_2NH \cdot HCl \quad (Ref. 42)$$

$$CH_3N(CH_3)_3 \cdot HCl \quad CH_3$$

In a few cases the products from Mannich reactions decompose spontaneously. Thus, from monoethyl ethylmalonate, formaldehyde, and diethylamine there is obtained directly ethyl α -ethylacrylate; undoubtedly, this is formed by elimination of carbon dioxide and diethylamine from the primary reaction product.⁴³

$$\begin{array}{c} \text{COOH} \\ \downarrow \\ \text{C}_2\text{H}_5\text{CHCOOC}_2\text{H}_5 + \text{H}_2\text{CO} + (\text{C}_2\text{H}_5)_2\text{NH}} \rightarrow \left[\begin{array}{c} \text{COOH} \\ \downarrow \\ \text{C}_2\text{H}_5\text{CCOOC}_2\text{H}_5 \\ \text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2 \end{array} \right] \\ + \text{H}_2\text{O} \rightarrow \text{C}_2\text{H}_5\text{CCOOC}_2\text{H}_5 + \text{H}_2\text{O} + \text{CO}_2 + (\text{C}_2\text{H}_5)_2\text{NH}} \\ \text{CH}_2 \end{array}$$

Other β -dimethylaminoketones are sufficiently unstable that they accompose in the presence of sodium ethylate or dilute alkaline solu-

⁴³ Mannich and Hönig, Arch. Pharm., 265, 598 (1927).

⁴¹ Mannich and Heilner, Ber., 55, 356 (1922).

⁴² Mannich and Bauroth, Ber., 55, 3504 (1922).

⁴¹ Mannich and Ritsert, Ber., 57, 1116 (1924).

tions. Addition of sodium carbonate to an aqueous solution of 2-nitro-β-dimethylaminopropiophenone hydrochloride or 3-acetylamino-β-dimethylaminopropiophenone hydrochloride results in an immediate liberation of dimethylamine.¹⁹

In some cases, when two carboxyl groups are present one is eliminated during the decomposition. a

This process, when a monosubstituted malonic acid is employed, serves as a satisfactory method for synthesizing various a-aryl- or a-alkyl-acrylic acids.

$$(\text{HOOC})_2\text{C}-\text{CH}_2\text{N}(\text{CH}_2)_1 \rightarrow \text{HOOCC}=\text{CH}_2 + (\text{CH}_4)_2\text{NH} + \text{CO}_2$$

Carter and Jones, in the preparation of a benzylacrylic acid, found refluxing the Mannich base in neutral aqueous solution to be an excellent method for the decomposition.

When the active hydrogen atom in the compound reacting with formaldehyde and a dialkylamine is a tertiary one, the product cannot decompose to an ethyleuse substance and bence, presumably, may decompose under hydrolytic conditions to the dialkylamine, formaldehyde, and the original compound. Thus is illustrated by the decomposihyde, and the original compound. Thus is illustrated by the decomposihyde, and the original compound. Thus is illustrated by the decomposihyde, and the original compounds that it is a substantial or an extension of the compound of th

Preparation of Pyrazolines. Another reaction that may depend on intermediate formation of an ethylenic compound is the production of pyrazolines by the action of phenythydrazine. Kohler ** demonstrated

[&]quot;H. F. Carter and R. C. Jones, private communication.

⁴ Kohler, Am. Chem. J., 42, 375 (1909).

that phenyl vinyl ketone and phenylhydrazine react with surprising ease to yield 1,3-diphenylpyrazoline.

$$C_6H_5COCH = CH_2 + C_6H_5NHNH_2 \rightarrow C_6H_5C \qquad NC_6H_5$$

When β -dimethylaminopropiophenone hydrochloride and phenylhydrazine react in the presence of sodium acetate, 1,3-diphenylpyrazoline is formed.^{13, 20, 40, 46, 47, 48} In some cases, the intermediate products must be treated with ethanolic hydrogen chloride to effect the cyclization.

It is not impossible that the initial phenylhydrazone decomposes to the phenylhydrazone of the phenyl vinyl ketone, which then cyclizes to the 1,3-diphenylpyrazoline. Such a mechanism is supported by the work of Nisbet, 49. 50. 51. 52 who observed that the phenylhydrazones of β -dialkylaminoketones derived from α,β -unsaturated ketones isomerize readily to pyrazolines and in so reacting make use of the double bond already present in the molecule.

Some of the 1,5-diaryl-3-(β -dialkylaminoethyl)-pyrazoline salts were shown by Nisbet 50, 51, 52 to be local anesthetics.

The Use of a Mannich Base as a Source of Unsaturated Ketone for Condensations with an Active Methylene Compound. A reaction which offers many possibilities in synthetic work is the condensation of β -dialkylaminoketones with active methylene compounds in the presence

⁴⁵ Jacob and Madinaveitia, J. Chem. Soc., 1929 (1937).

⁴⁷ Harradence and Lions, J. Proc. Roy. Soc. N. S. Wales, 72, 233 (1938).

⁴⁵ Harradence and Lions, J. Proc. Roy. Soc. N. S. Wales, 73, 14 (1939).

O Nisbet and Gray, J. Chem. Soc., 839 (1933).

⁵⁰ Nisbet, J. Chem. Soc., 1237 (1938).

¹¹ Niebet, J. Chem. Soc., 1568 (1938).

⁴² Levry and Nisbet, J. Chem. Soc., 1572 (1938).

of sodium ethovide. Apparently a gradual formation of $\alpha\beta$ -unsaturated betone results in a smoother addition reaction than is possible when the $\alpha\beta$ -unsaturated ketone is used directly in the Michael condensation. For example, by a condensation with accloactic ester Mannich 12 converted 2-dimethylaminomethyleyelohexanone to a β -decalone derivative in excellent yield; the product was subsequently degraded to β -decalone.

Robinson's has employed a modification of this procedure for the synthesis of a variety of compounds which are otherwise inaccessible. The modification consists in treating the Mannich base with methyl foldied. A solution of the methiodide, which need not be isolated, is allowed to react with the active methylene compound in the presence of sodium amide or sodium ethovide. The advantage of the methiodide over the Mannich base presumably lies in the liberation of the $\alpha_s \beta$ unsaturated ketone at lower concentration and greater reactivity. The following two syntheses illustrate Robinson's modification.

Mannich, Koch, and Borkowsky, Ber., 70, 355 (1937).

$$\begin{array}{c} \text{CH}_{2} \\ \text{CH}_{2} \\ \text{CH}_{2} \\ \text{N} \\ \text{C}_{2} \\ \text{H}_{5} \\ \text{)}_{2} \\ \text{CH}_{3} \end{array} + \text{CH}_{2} \\ \text{COCH}_{2} \\ \text{CO}_{2} \\ \text{C}_{2} \\ \text{H}_{5} \\ \text{CO}_{2} \\ \text{CO}_{3} \\ \text{CO}_{4} \\ \text{CO}_{4} \\ \text{CO}_{4} \\ \text{CO}_{5} \\ \text{CO}$$

Conversion of a Ketone to Its Next Higher Homolog. Reduction of the unsaturated ketone obtained by decomposition of a Mannich base leads to a ketone with one more methylene group than that used in the preparation of the Mannieh base.¹¹

Syntheses Dependent on the Active Methylene Group in the Aminoketone

Advantage can be taken of the active methylene group in the β -dialkylamino carbonyl compounds for the synthesis of products otherwise inaccessible. Thus β -dimethylaminocthyl methyl ketone and o-nitrobenzaldehyde react to give a product which upon reduction loses water to form a substituted quinoline.⁵⁴

CHO
$$+ H_{2}C - CH_{2}N(CH_{2})_{2} \rightarrow COCH_{3}$$

$$+ H_{2}C - CH_{2}N(CH_{3})_{2}$$

$$+ H_{2}C - CH_{2}N(CH_{3})_{2}$$

$$+ H_{2}C - CH_{2}N(CH_{3})_{2}$$

$$+ H_{2}C - CH_{2}N(CH_{3})_{2}$$

$$+ CH_{2}N(CH_{2})_{2}$$

$$+ CH_{2}N(CH_{3})_{2}$$

$$+ CH_{2}N(CH_{3})_{2}$$

An analogous reaction may be used for the preparation 2- $(\beta$ -piperidinethyl)-6,7-methylenedioxyquinoline.

¹⁴ Mannich and Reichert, Arch. Pharm., 271, 116 (1933).

¹⁴ Mannich and Schilling, Arch. Pharm., 276, 582 (1938).

Syntheses Dependent on the Activity of the Dimethylamino Group in Dimethylaminomethylphenols

The products obtained by the Mannich reaction with phenols have possible synthetic uses in the introduction of methyl groups into the phenolic ring. Thus, β-dimethylaminomethylxylenol is readily hydrogenolyzed to 2,3,5-trimethylphenol.24

$$\operatorname{CH}_1 \xrightarrow{\operatorname{OH}} \operatorname{CH}_1 \xrightarrow{\operatorname{CH}_1} \operatorname{CH}_2 \xrightarrow{\operatorname{CH}_2} \operatorname{CH}_1 \xrightarrow{\operatorname{CH}_1} \operatorname{CH}_1$$

It has also been demonstrated that when these phenolic substances are treated with acetic anhydride the dimethylamino groups are replaced by acetoxy groups, 2,4,6-Tri-(dimethylaminomethyl)-phenol is converted into 2,4,6-tri-(acetoxymethyl)-phenyl acetate.

$$(\operatorname{CH}_3)_2\operatorname{NCH} \underbrace{ \begin{array}{c} \operatorname{OH} \\ \operatorname{CH}_2\operatorname{N}(\operatorname{CH}_3)_2 \\ \end{array}}_{\operatorname{CH}_2\operatorname{NCOCH}_3} \underbrace{ \begin{array}{c} \operatorname{COCCH}_3 \\ \operatorname{CH}_2\operatorname{COCCH}_4 \\ \end{array}}_{\operatorname{CH}_3\operatorname{COCCH}_3}$$

Reduction to Aminoalcohols

The β -substituted aminoactories or aldehydes can be reduced readily to the corresponding 7-substituted aminoalkanols, It which are much more stable than the corresponding ketones. This procedure provides an unusually good source of such aminoalcohols. When the ketone contains an asymmetric carbon atom a second one is introduced when the carbinol is formed, and in several cases the two diastereoisomeric modifications have been isolated. 1. 15. 25. 46. 47. 55. 57. 60

The γ-aminoalcohols, in the Iorm of their benzoates and p-aminobenzoates, find application as local anesthetics, and many such physiclogically active compounds have been prepared through the Mannich reaction s. u. 16, 27, 40, 41, 25, 27, 61, 65, 63 The commercial local anesthetic Tutocaine is made from the alcohol obtained by reduction of the Mannich base from dimethylamine, formaldchyde, and ethyl methyl ketone;

- Mannich and Curtas, Jrch. Pharm., 264, 741 (1926).
- Mannich, Arch. Pharm., 263, 251 (1927). 15 Mannich, Borkowsky, and Ian, Arch, Pharm., 273, 51 (1937).
- 19 Mannich and Salamann, Ber., 72, 506 (1939). Mannich and Stein, Arch. Pharm., 264, 77 (1926).
- 11 Mannich and Schaller, Arch. Phys., 216, 575 (1918). 44 Mannich and Hof, drek, Phore., 265, 589 (1927)
- Manpich and Horkheimer, Arch, Pharm, 254, 167 (1926).

the alcohol is converted to the p-aminobenzoate, and the latter is used as the hydrochloride.

Products Derived by Transformation of the Aldehyde Group in β-Dialkylaminoaldehydes

Certain of the β -dialkylaminoaldehydes can be transformed into piperidine derivatives. Thus, α,α -dimethyl- β -dimethylaminopropionaldehyde is converted into 1,2,5,5-tetramethylpiperidine.²³

$$\begin{array}{c} \text{CH}_{3} \\ \text{CH}_{2}\text{C} \\ \text{CH}_{0} \\ \text{CH}_{1}\text{C} \\ \text{CH}_{0} \\ \text{CH}_{2}\text{C} \\ \text{CH}_{0} \\ \text{CH}_{2}\text{C} \\ \text{C} \\ \text{CH}_{2}\text{C} \\ \text{CH}_{2}\text{C} \\ \text{C} \\ \text{C} \\ \text{$$

The aminoaldehyde also may be transformed into the corresponding amino acids 15 by the following series of reactions.

$$(CH_{2})_{2}C - CHO \rightarrow (CH_{2})_{2}C - CH = NOH \rightarrow$$

$$CH_{2}N(CH_{2})_{2} \qquad CH_{2}N(CH_{2})_{2}$$

$$(CH_{2})_{2}C - CN \rightarrow (CH_{2})_{2}C - COOH$$

$$CH_{2}N(CH_{2})_{2} \qquad CH_{2}N(CH_{2})_{2}$$

β-Monoalkylaminoketone Condensation Products

The Mannich bases from one molecule of a primary amine, one of formaldehyde, and one of ketone have been used in a variety of condensations involving both the ketone group and the secondary amine group. The nitreso derivative of β -methylaminopropiophenone is readily reduced to the corresponding β -hydrarinoketone, which cyclizes to 1-methyl-3-pheneylpyraroline.⁴⁴

$$\begin{split} \text{C}_{4}\text{II}_{4}\text{COCH}_{2}\text{CH}_{3}\text{NHCH}_{3}\text{-HCl} &\rightarrow \text{C}_{4}\text{II}_{4}\text{COCH}_{5}\text{CH}_{3}\text{N}-\text{CH}_{4} &\rightarrow \\ &\text{NO} \\ \\ \text{C}_{4}\text{H}_{4}\text{COCH}_{5}\text{CH}_{5}-\text{NCH}_{4} &\rightarrow \\ &\text{C}_{4}\text{H}_{5} &\text{C}_{4}\text{H}_{5} \\ &\text{NCH}_{5} &\text{NCH}_{5} \\ \\ &\text{NH}_{5} \end{split}$$

A similar cyclization occurs in the formation of 2-benzyltetrahydronaphthindazole 15 by reduction of 2-(benzylnitrosaminomethyl)-α-tetralone.

Other types of cyclic compounds may result if properly constructed molecules and appropriate reagents are used. Thus the compound from benzylamine hydrochloride, formaldehyde, and cyclobexanone reacts with potassium cyanate to form a urea which undergoes dehydration to an octahydroquinasofine.³³

$$\begin{array}{c} CH_1NHCH_2C_4H_4 \\ O\\ O\\ O\\ H_2N \end{array} \xrightarrow[]{CH_2} CH_4 \\ CH_3\\ CCH_4\\ $

Mannich and Heiner, Ecr., \$5, 365 (1922).

An analogous reaction has been used for the synthesis of 1-methyl-2-keto-1-phenyl-1,2,5,6-tetrahydropyrimidine from β -methylaminopropio-phenone.

Condensation Products from One Mole of a Primary Amine, Two Moles of Formaldehyde, and Two Moles of a Ketone

Benzylamine hydrochloride, formaldehyde, and acetophenone react to form a mixture of products: ²¹ the first from one mole of benzylamine, one of acetophenone, and one of formaldehyde; and the second from one mole of benzylamine, two of acetophenone, and two of formaldehyde. The second is unstable and cyclizes to a piperidine derivative.

$$C_{\epsilon}H_{\epsilon}COCH_{2} + HCHO + C_{\epsilon}H_{\epsilon}CH_{2}NH_{2} \cdot HCI \rightarrow$$

C.H.COCH.CH.NHCH.C.H.·HC!

 $2C_{\epsilon}H_{\epsilon}COCH_{\epsilon} + 2HCHO + C_{\epsilon}H_{\epsilon}CH_{\epsilon}NH \cdot HCI \rightarrow$

Benzylamine hydrochloride condenses similarly with cyclohexanone,³⁵ and the product involving two moles of cyclohexanone is converted to a reduced isoquinoline derivative during the reaction.

$$\begin{array}{c} 0 \\ \text{CH}_2 \\ \text{NCH}_2\text{C}_{\ell}\text{H}_{\bar{z}} \cdot \text{HCI} \end{array} \rightarrow \begin{array}{c} 0 \\ \text{OH}^{\text{CH}_2} \\ \text{NCH}_2\text{C}_{\ell}\text{H}_{\bar{z}} \cdot \text{HCI} \end{array}$$

A tricyclic ring system is formed when the diethyl ester of 1-methyl-3,5-diallyl-1-piperidone-3,5-dicarboxylic acid (obtained from the diethyl

ester of \alpha, \alpha'-dially acctonedicarboxylic acid, two moles of formaldehyde, and one of methylamine) is hydrolyzed and decarboxylated.32

EXPERIMENTAL CONDITIONS AND PROCEDURES

Solvents

When aqueous formaldehyde is used the condensation is ordinarily carried out by shaking or stirring the reactants in the absence of an organic solvent: in some cases ** methanol has been added to such mixtures. When paraformaldehyde is used an organic solvent is required. If the ketone component is a liquid, such as acctone.29 cyclopentanone,47 or eyelohexanone,47 an excess of it may be used as the solvent. In other cases ethanol (95% or absolute) is added as the In condensations involving 2-, 3-, or 9-acetylphenanthrene, solvent. paraformaldehyde, and salts of secondary amines, isosmyl alcohol is recommended as the solvent.45 The condensations proceed much faster in the higher-boiling solvent, and the formation of certain by-products. obtained by prolonged heating in ethanol, is avoided. On the other hand, it is stated that, although in ethanol the condensation between 3-acetyl-9-methylcarbazole, formaldehyde, and a secondary amine salt proceeds more slowly than in isoamyl alcohol, it is less subject to side reactions associated with instability of the aminoketone salts at the higher temperature. 45

Nature of Formaldehyde and Time of Reaction

Formaldehyde is used in the form of a 20-40% aqueous solution or as paraformaldehyde. In certain reactions, such as the condensation of a-tetralone, formaldehyde, and tetrahydroisoquinoline hydrochloride. aqueous formaldehyde is said to be superior to paraformaldehyde.16

In a few cases 12. 15. 47 enough concentrated hydrochloric acid is added at the beginning of the reaction to make the mixture acidic to Conso red:

⁴⁴ wan do Kamp and Mosettig, J. Am Chem. Soc., \$3, 1563 (1936). 44 Ruberg and Small, J. Am. Chem. Soc., 63, 736 (1941).

in other instances 11, 15, 65 the mixture is acidified at the end of the reaction in order to depolymerize unchanged paraformaldehyde and bring it into solution.

The time required for a Mannich reaction depends upon the nature of the ketone and of the amine salt and upon the boiling point of the solvent employed. The reaction between furfuralacetone, paraformal-dehyde, and dimethylamine hydrochloride in alcoholic solution is said to be complete after the mixture has been boiled for a few minutes.⁴² When 3-acetyl-9-methylcarbazole, paraformaldehyde, and diethylamine hydrochloride are heated in absolute ethanolic solution for five hours the yield of reaction product is 59% but is increased to 83% when the mixture is heated for eight hours.⁶⁵

Relative Amounts of Components

In the preparation of Mannich products, various investigators have mixed the components in the calculated quantities or they have employed an excess of the amine salt and formaldehyde or an excess of the ketone. It is common practice to use 1.00 molecular equivalent of the carbonyl compound, 1.05–1.10 molecular equivalents of the amine salt, and 1.5–2.0 molecular equivalents of formaldehyde. Excellent yields of the basic ketone are obtained by the interaction of cyclohexanone, aqueous formaldehyde, and dimethylamine hydrochloride, or morpholine hydrochloride, when five times the calculated quantity of ketone is allowed to react. When excess formaldehyde is used, the material is added in several portions during the course of the reaction. Part of the formaldehyde reacts with ethanol, when this is used as a solvent, to form methylene diethyl ether.

Due consideration should be given to the manner in which unchanged amine salt and formaldehyde can be separated from the desired product at the termination of the reaction. If difficulties are anticipated in such separations, the advantage to be gained by the employment of any of the components in excess may be questioned. If more than one reaction product is possible, the relative amounts of amine salt and formaldehyde may or may not influence the nature and yield of the product.^{15, 15}

Isolation of Product

In a number of cases the salt of the desired product precipitates when the reaction mixture is cooled. Ether may be added to facilitate separation of the product. Occasionally the solvent is removed and crystallization of the residue brought about by washing it with ether or acetone. Sometimes it is advantageous to liberate the basic product from its salt and purify the former by distillation, provided that the material can be distilled without decomposition.

By-Products

By-products of the reaction have been identified in some instances. They may be formed by some change of the reaction product liself, or they may be produced by condensation of the formaldetiyle with the amine or ketone. Thus, dicthylamine may be converted to N₁N²-tetrachtylmethylenedizanic, and pipriodine to methylenedizanichine. From reactions involving cyclohexanone, there have been isolated 2-methylene cyclohexanone "and di-cyclohexanonyimethyl) ether." Similarly, methylenedizanichine have been isolated by the been produced in reactions involving β-naphthol and antipyrine, respectively.

Procedures

Preparation of Pienryl \$\beta\$-Piperidinecthyl Ketone Hydrochloride, \$\mathbb{\tilde{\mathbb{\

1-Keto-2-(1,2,3,4-tetrahydroisoquinotinomethy)-1,2,3,4-tetrahydroisoquinotinomethy)-1,2,3,4-tetrahydroisoquinotinomethy)-1,2,3,4-tetrahydroisoquinotine nydrocthoride is prepared in a small (preferably 50-c.) three-necked flask equipped with mechanical stirrer, a reflux condenser, and a tube for admission of nitrogen. A slow stream of nitrogen a paseed through the appearants while the mixture is stirred and heated on the steam both for one and one-half hours. The brown viscous mass is dissolved in water, and the solution is freed of neutral substances by extraction with ether. Concentrated ammonium hydroxide is then added to the aqueous solution until no further separation of water-insoluble material occurs. The product is collected by extraction with ether. The residue obtained by distillation of the ether solidifies upon washing with cold chand. Recrystallization of the etner solidifies

(7.4 g.) from the minimum quantity of ethanol yields 6.6 g. (66%) of the pure aminoketone, m.p. 90-91°.

2,4,6-Tri-(dimethylaminomethyl)-phenol. A mixture of 94 g. (1 mole) of phenol and 720 g. (4 moles) of 25% aqueous dimethylamine solution is cooled to 20° in a 2-l. three-necked flask fitted with a stirrer, a thermometer for reading the internal temperature, and an addition funnel. The mixture is stirred while 350 g. of 30% aqueous formal-dehyde is added dropwise over a period of about one-half hour, the reaction mixture being maintained at 25–30°. Stirring at this temperature is continued for one hour after completion of the addition. The addition funnel is then replaced by a reflux condenser, and the solution is stirred and heated on a steam bath for two hours. To the hot solution is added 200 g. of sodium chloride, and stirring and heating are continued for about twenty minutes.

The organic layer is separated from the hot solution and transferred to a 500-cc. Claisen flask. It is distilled under diminished pressure; the fraction boiling at 130-150°/1-2 mm. weighs 228 g. (86%). The slight red color can be removed by redistillation (b.p. 130-135°, 1 mm.) with almost no loss.

EXAMPLES OF THE MANNICH REACTION*

The reactions summarized in Table V are classified according to the complexity of the basic component of the reaction mixture. Thus, reactions involving ammonia or its salts are listed first, and those involving secondary amines or their salts, last. Only the name or formula of the aminoketone is given in the product column; in reactions involving amine or ammonium salts it is to be understood that the product is also a salt. The yields are those given in the literature; sometimes they refer to purified products, sometimes to crude materials. Undoubtedly, many of the yields could be improved by a thorough study of optimum reaction conditions and processes of isolation and purification.

^{*} Attention should be called to the very interesting manner in which a CH₂NR₂ group has been introduced into acetophenone 66 , 2.4-dinitrotoluene 96 , α - 90 and 2-naphthol 95 , α - 95 and p-cresol 25 , α - 95 and 3-naphthylamine 95 by the use of a basic ether R—O—CH₂NR₂.

McLeod and Robinson, J. Chem. Son., 119, 1470 (1921).

⁶⁷ Heor-Feo Tseou and Chang-teing Yang, J. Orp. Chem., 4, 123 (1933).

TABLE V *

Reactante	Product (Yield)
Ammonia, formalitehyde, and	HOC(COORI ₂ CH ₂ NR ₄ (39%)
Tartronic acid **	CallaCliaC(COOII)aCliaNila (65%)
Bensylmalonic and 10	to the the cremottise Classical (58%)
Phenylmalonie acud 12	CallaCH(COOH)CH, NII (63%)
Ammonia, bensaldshude, and	Chipmin
Dimethyl (and diethyl) accions	
dicarbox late 44	Dimethyl [and diethyl) 2,6-diphenyl-1-piperidone-3,5-dies
and souprate :	boxylate (good)
Ammonsum sklorute, formalitekyte,	
and	1.4 Damethyl-3 acetyl-4-hydroxypiperidina ()
Acetona 18, 29	1,3-Trimethyl-4-piperidone (29) (—)
Disthyl ketone 29	
Acetophenona 5: 54	1-(s-Bensoylethyf)-3-bensoyl-4-bydroxy-4 phanylpiperidine
	To the alcherencey impthyl) - amina (-)
Cyclohexanona 17	
Antipyrine 5	
p-Tolypyrina *	
Homoantipyrine 5	[CallaCit(Cooli)CitalaNit (65%)
Phenylmalonic seid 12	Chitomer
Ammonium bromide,† acetalitekyde, and	1 . 1 - md sto (46 5.55)
Diethyl acetonodicerbosylate 25	Duethyl 2,6-dimethyl-4-piperidone-1,5-dicarboxylete (46 5%)
Methylamine, formaliehyde, and	
Tartronie acid 11	HOC(COOID;CH;NHCH; (33%)
Methylmalonic erel, 1 ti	[CH ₂ C(COOID ₂ CH ₂) ₃ NCH ₂ (31%)
Lthyimalong arid 15	CilictiaC(COOII)aCiliNIICila (-) CilictiaC(COOII)aCiliNIICila (very good)
Beneylmalonio and ta	
Phenacylmalonic acid 12	(4)No ₂ Call ₄ Cil(Cooll)Cil ₄ NilCil ₄ (20%)
4-Nutrophenylacetic eral #7	
Diethyla,a'-diethylaretonedicar-	Dicthyl I-methyl-3,5-dicthyl-1-paper idens-3,5-dicarboxylsta
boxylate 22	(40%)
	(40 g)
Diethyl a,a'-dully lacetonedicar-	Durthyl I-methyl-3,5-duallyl-4 papersions-3,5-durarboxylata
boxylata ==	(65-70°E)
Diethyl 2,6-dimethyltetrahydro-	
pyrone-3,5-dicar bonylata 12	A "pyrdux" § (64"2)
Diethyl 2,5-diphenyltetrahydro-	A 'pydm'' (>80%)
pyrone-3.5-dicarboxylata si	A 'pydm' (>80/s/
Demothyl Lengthyl-2.6-diphenyl-	A 'bespedin' \$ (74%)
4 niperidone-3.5-dicar boxylate 24	
Dimethyl 1-allyl-2,6-diphenyl-	A "bispedes" # (70%)
4-paperidone-3,5-dicarbosylatass	
Dimethyl tropanone-2,4-dicar-	A tranyche compound \$ (45-50%)
bosylate 23 Methylamine, bensaldchyde, and	
Dimethyl (and diethyl) acetone-	Demethyl (and dethyl) 1-methyl-2,8-dephenyl-4-paperidon
	Dimethyl (and diethyl) 3,5-drarboxylate (65%)
	3,5-drearborgists (65%) 3,5-drearborgists (65%) 3,5-drearborgists (65%) 3,5-drearborgists (65%) 3,5-drearborgists (65%) 4,5-drearborgists (65%) 5,5-drearborgists (65
& Deferences 67-74 appear not p 3	41 when amount when ammonium chloride was used in piace.
The piperidone was obtained in	still lower when ammonia was substituted for an
ammonium bromide, the youdent	fied product

Reactants	Product (Yield)
Methylamine hydrochloride, formal-	
dehyde, and	
Acetone 29, 14	(CH ₂ COCH ₂ CH ₂) ₂ NCH ₃ (56%)
	1.4-Dimethyl-3-acetyl-4-hydroxypiperidine (—)
Diethyl ketone	CH ₂ CH ₂ COCH(CH ₂)CH ₂ NH(CH ₂) (—)
	1,3,5-Trimethyl-1-piperidone (—)
	CH ₂ CH[CH ₂ NH(CH ₂)]COCH[CH ₂ NH(CH ₂)]CH ₂ or
	CH ₂ CH ₂ COC[CH ₂ NH(CH ₂)] ₂ CH ₄ (—)
Acetophenone 41, 10	[CH ₂ CH ₂ COCH(CH ₂)CH ₂] ₂ NCH ₂ (—) C ₂ H ₂ COCH ₂ CH ₂ NHCH ₂ (70%)
Regrophenghe	(C _t H ₁ COCH ₂ CH ₂ NCH ₂ (34%)
Cyclohexanone 27	Methyldi-(2-cyclohexanonylmethyl)-amine (2.4%+)
2-Acetylthiophene 12	Methyl di-[2-(a-thenoyl)-ethyl]-amine (61%)
Antipyrine 17	Methyldi-(4-antipyrylmethyl)-amine (92%)
Isobutyraldebyde 20	(CH ₂) ₂ C(CHO)CH ₂ NHCH ₂ (70%)
Dimethyl (and diethyl) 1,2,6-tri-	(
methyl-4-piperidone-3,5-dicar-	
borylate 2	A "bispidin" (70%)
Methylamine hydrochloride, acetal-	
dehyde, and	
Diethyl acetonedicarboxylate 23	Diethyl 1,2,6-trimethyl-1-piperidone-3,5-dicarboxylate (—)
Ethylamine, benzaldehyde, and	
Diethyl acetonedicarboxylate (2	Diethyl 1-ethyl-2,6-diphenyl-4-piperidone-3,5-dicarboxy- late (—)
Ethylamine hydrochloride, formolde-	
hyde, and	Til litte in the same of the s
2-Methyl-S-nitroquinoline 23	Ethyldi-[6-(8-nitro-2-quinolyl)-ethyl]-amine ()
Antipyrine ¹⁷ 8-Hydroxyethylamine, benzaldehyde,	Ethyldi-(4-antipyrylmethyl)-amine (—)
and	
Dimethyl acetonedicarboxylate 24	Dimethyl 1-(\$-hydroxyethyl)-2,6-diphenyl-4-piperidone-3,5- dicarboxylate (65%)
β-Chloroethylamine hydrochloride,	
formaldehyde, and Dimethyl 1,2,6-trimethyl-4-pi-	
peridone-3,5-dimrboxylate #	A "bispidin" (63%)
B-Phenylethylamine hydrochloride,	en anagratitat (OO)(C)
formaldehyde, and	
Dimethyl 1,2,6-trimethyl-4-pi-	
peridone-3,5-dicarboxylate #	A "bispidin" (—)
β-Phenylethylamine hydrochlonde, †	
acetaldehyde, and	
Dimethylacetonedimentorylate p	Dimethyl 1-(\$\beta\$-phenylethyl)-2,5-dimethyl-1-piperidone-3,5-dimethyl-1-piperidone-3,5-
Allylamine, formaldelyde, and	CHOLOGOD ON MAN ON A
Bensylmalonic acid D Dimethyl 1-methyl-2,6-diphenyl-	C _t H ₁ CH ₂ C(COOH) ₂ CH ₂ NHCH ₂ CH=CH ₂ (good)
4-piperidone-3,5-dicarboxylate 3	A "bispidia" (75%)
Allularine, bermildehule, and	TO DOUBLE (TO JE)
Dimethyl socionedicarboxylate H	Dimethyl 1-allyl-2,8-diphenyl-4-piperidone-3,5-dicarboxylate (70%)

^{*} References 67-74 appear on p. 341
† Neither the tavenue not the dexizo or levo modification of a-phenylethylamine hydrochloride could be made to react with acctaldehyde and the ester of acctonedicarboxylic acid.

Reactants	Product (Yield)
Allylamine, sniedlichyde, and	
Dunethyl acetonedicarboxylate H	Dimethyl 1-allyl-2,6-di-p-annyl-4-paperidone-3,5-dicarboxyla
Allylamine hydrockloride, formalie-	1
Aprile, and	í
Dimethyl 1,2,6-trimethyl-4-pi-	
peridone-3,5-dicarboxylate #	A "hepdin" (-)
Antipyrine 11	Allyble-(&-entrpyry lmethyl)-amine ()
or Aminocetophenous kydrockloride,	
formalickyde, and	
Antipyrine (7	CallaCOCHaNRs, R = 4 antipyrylmethyl (98%)
Ethyl amsnoaretate hydrochloryde,	
formaldehyde, and	
Antipyrine (?	RancilacogCalla. II = 4-antipyrylmethyl (-)
Brandamine, phonylacetaldehyde, and	
Cyclohezanone #	CattaCffaNHCff(CffaCaffa)CallaO (1.5%)
Brazilanina kpirochiarsia, famali-	Chileria mentende de como (1 4/1)
dehade, and	ſ
Acetone M	CHI-COCH-CH-NHCH-C-III- (>3%)
Beeralacetone #	Call-Cil=CilCocil_Cil_NilCil_Call_(20%)
executaristations -	1.Bensyl-3-manamyi-4-styryi-4-bydrogypipendine (10%)
Acetophenone #	CallaCOCHaCHaNHCHaCattle (53%)
**Cesophenone -	1-Beast-3-beason14-phenyl-4-hydroxymperidine (-)
Cyclopentanone #	Bengal-(2-cyclopentanony/methyl)-aming (-)
Cycloberanone #	Reneyl-(2-cycloheranoaylmethyl)-amine (65%)
CALIGRATHINGS -	A decabydrousquastine (10-25%)
n-Tetralone 21	# (Beneylamunomethyl)-etetralone (\$5%)
Bennylamina hydrachlorule, acetalde	
hade, and	
Dimethyl scetonedicarbosylets*	Damethyl 1-bensyl-2,6-damethyl-1-pipersions-3,5-dam/boxylate (20%)
3.4-Methylenedioxybensylamine	
hydrochloride, formaldskyde, and	The second Off second C fr an American
Acrices **	CH_COCH_CH_NHCH_C_H_(O_CH_)(3,4) (20%) C_H_CH=CHCOCH_CH_NHCH_C_H_(O_CH_)(3,4) (52%)
Bensalecetone 35	C ₄ H ₃ CCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ (C ₃ CH ₃ (C ₃ C) C ₄ H ₃ COCH ₂ CH ₃ NHCH ₂ C ₄ H ₃ (C ₃ CH ₃ (C ₃ C) C ₄ H ₃ COCH ₂ CH ₃ NHCH ₂ C ₄ H ₃ (C ₃ CH ₃ (C) ₃ C) C ₄ H ₃ CCH ₃ CH ₃ NHCH ₂ CH ₃ (C ₃ CH ₃ (C)
Acetophenous 55	CallyCocketContours (Optile)(3,4) (56%) 2 (3,4-Methylenediourbeneylaminomethyl)-cyclopentanons
Cyclopentanone **	
	(67%) 2-(3,4-3fethylmodioxybennylammomethyl)-cyclohexanone ()
Cyclohexanone 25	A decalirations of the temperature of ()
	\$-(3.4-Methylauodoxybonzylammomethyl)-e-tetralone (70%)
e-Tetraline is	b-(a'b-uern) arman and arman americal Metricity around (10 %)
Anilene, benealishyde, and	1.2.6-Tophesyl 4-psperidone ()
Acetona ed	
Tetrahydro-B-maphthylamine kydro-	
hloride, formaldehyde, and	Tetrahydro-S-maphthykli-(f-antipyry/methyl)-amine ()
Antipyriae 17 Ethylenodiamine hydrochloride,	
Ethylenodiamine nysracia	
formaldehyde, and	Tetra-(4-antipyrylmethyl)-ethylenediamize (77%)
Antipyrine 17	

Reference 67-74 appear on p. 341.
 See p. 326.

EXAMPLES OF THE REACTION

Exa	IMPLES OF THE REACTION		
Reactants	Product (Yield)		
Dimethylamine, formaldehyde, and			
Cyanoacetic acid 19	CNCH ₂ CH ₂ N(CH ₃) ₂ † (—)		
4-Nitrophenylacetic acid 67	(4) NO ₂ C ₆ H ₄ CH(COOH)CH ₂ N(CH ₂) ₂ (67%)		
2,4-Dinitrophenylacetic acid 67	(2,4)(NO ₂) ₂ C ₆ H ₂ CH[CH ₂ N(CH ₂) ₂] ₂ (52%)		
Benzoylacetic acid ss	CeH ₅ COCH ₂ CH ₂ N(CH ₃) ₂ (—)		
	(CH ₂) ₂ NCH ₂ CHCOCOOCH ₂ \$ (56%)		
Pyruvic acid ²⁰			
Acetoacetic acid	CH ₂ COCH ₂ CH ₂ N(CH ₂) ₂ (42%)		
	CH ₂ COCH[CH ₂ N(CH ₂) ₂] ₂ (28%)		
Methylacetoacetic acid	CH ₂ COCH(CH ₂)CH ₂ N(CH ₂) ₂ (—)		
Ethylacetoacetic acid 20	$CH_2COCH(C_2H_5)CH_2N(CH_2)_2 \ddagger (30\%)$		
Allylacetoacetic acid	CH2COCH(CH2CH=CH2)CH2N(CH3)2 (38%)		
Levulinic acid 20	(CH ₂) ₂ NCH ₂ CH ₂ COCH ₂ CH ₂ COOH ‡ (21%)		
Malonic acid 21	CH(COOH)[CH ₂ N(CH ₂) ₂] ₂ (47%)		
Methylmalonic acid 21	CH ₂ C(COOH) ₂ CH ₂ N(CH ₂) ₂ (55%)		
Ethylmalonic acid 12	CH ₂ CH ₂ C(COOH) ₂ CH ₂ N(CH ₂) ₂ (70%)		
Allylmalonic acid 12	CH2=CHCH2C(COOH)2CH2N(CH2)2 (90%)		
Benzylmalonic acid 12	C _t H ₂ CH ₂ C(COOH) ₂ CH ₂ N(CH ₂) ₂ (90%)		
Phenylmalonic acid 13	C ₂ H ₂ CH(COOH)CH ₂ N(CH ₂) ₂ (60%)		
7-Phenylpropylmalonic scid 19	CeHaCH2CH2CH2C(COOH)2CH2N(CH2)2 (99%)		
Phenacylmalonic acid 19	C ₂ H ₂ COCH ₂ C(COOH) ₂ CH ₂ N(CH ₂) ₂ (45%)		
Tartronic acid 42	HOC(COOH) ₂ CH ₂ N(CH ₂) ₂ (54%)		
Ethanetricarboxylic acid 12	(HOOC) ₂ C(CH ₂ COOH)CH ₂ N(CH ₂) ₂ (46%)		
Phenylacetylene 25	$C_2H_2C \equiv CCH_2N(CH_2)_2$ (—)		
	$(2) NH_2C_cH_4C \equiv CCH_2N(CH_2)_2 ()$		
2-Aminophenylacetylene 25	4-Dimethylaminomethylantipyrine (60%)		
Antipyrine 6 Phenol 21, 22, 22	2-(Dimethylaminomethyl)-phenol (—)		
Phenol 24 ****			
	2.6-Di-(dimethylaminomethyl)-phenol (poor)		
	2,4,6-Tri-(dimethylaminomethyl)-phenol (86%)		
4-Acetylaminophenol 21	2-(Dimethylaminomethyl)-4-acetylaminophenol ()		
o-Cresol ==	2-(Dimethylaminomethyl)-6-methylphenol ()		
m-Cresol ==	2,4,6-Tri-(dimethylaminomethyl)-3-methylphenol (—)		
p-Cresol #	2-(Dimethylaminomethyl)-4-methylphenol ()		
	2,6-Di-(dimethylaminomethyl)-4-methylphenol (-)		
2-Methoxyphenol 25	2-Methoxy-6-(dimethylaminomethyl)-phenol (—)		
4-Methoxyphenol 23	4-Methoxy-6-(dimethylaminomethyl)-phenol (-)		
3,5-Dimethylphenol 26	2-(Dimethylaminomethyl)-3,5-dimethylphenol (34%)		
2-Methyl-4-ethylphenol ==	2-Methyl-4-ethyl-6-(dimethylaminomethyl)-phenol ()		
Catechol 25	Dimethylaminomethylcatechol (-);		
Resorcinol 25	Dimethylaminomethylresoreinol (—):		
Hydroquinone 24, 25	2,5-5/4-(Dimethylaminomethyl)-hydroquinone (almost quanti- tative) 1		
Phloroglucinal =	Dimethylaminomethylphloroglucinol (—): br=(Dimethylaminomethyl)-phloroglucinol (—):		
Indole 74,744	3-Dimethylaminomethylindole (almost quantitative)		
p-Naphthol 25	Dimethylaminomethyl-β-naphthol (—)		
Dimethylamine hydrochloride, form-			
aldehode, and			
Acetone 27, 13	CH2COCH2CH2N(CH2)2 1 () (1472)		
ASCENSIA.	CH2COCH(CH2N(CH3)22 1 (-) (\$577)		
Methyl ethyl ketone et	CH-COCH(CH ₂)CH ₂ N(CH ₃) ₂ ()		
Date and the second	Cu ₂ Cu ₂ CoCu ₂ Cu ₁ N(Cu ₂) (-)		
Methyl propyl ketone er	CH1COCH(C2H1)CH1N(CH1)2 (-)		
March Strabby and and and and and and and and and and			

[#] References 67-74 appear on p. 341.

The product could not be obtained in enviralline form.
In this instance the amore salt was employed.
The amore base was used.

EXAMPLES OF THE REACTION

	7			
Resctanta	Product (Yield)			
Diethyl ketone to	CR4CH4COCH(CR4)CH4N(CH4)4 (31%)			
Acetophenone 42	C ₂ H ₂ COCH ₂ CH ₂ N(CH ₂) ₂ (40%)			
2-Nitrascetophenons #	(2) NO ₂ C ₄ H ₄ COCH ₂ CH ₂ N(CH ₄) ₁ (80-90° ₄)			
3-Nitroacetophenone 13	(3) NO ₂ C ₄ H ₄ COCH ₂ CH ₂ N(CH ₂) ₁ (80–90%)			
3-Acets famingeretonhanona 12				
3-Beoroy laramos returbanena la	(3)(CaHaCONH)CaHaCOCHaCHaN(CHa)a (79%)			
	(4)CH4OC4H4COCH4CH4N(CH4)4 ()			
Avetoveratrone 11	(3.4)(CR ₂ O) ₂ C ₄ H ₂ COCH ₂ CH ₃ N(CH ₂) ₄ ()			
Recualeretone 30, 84	CallaCH=CHCOCHaCHaN(CHaba (23%)			
4-Anualecetone to	(OCH,OC,H,CH=CHCOCH,CH,N(CH,), (63%)			
Piperchalacetone It	(3,4)(CH ₂ O ₂)C ₄ H ₂ CH ⇒CHCOCH ₂ CH ₂ N(CH ₂) ₄ (→)			
3- Vethory-s-ethorybenralace-	(stotedopointed sentoculents (empi (=)			
	(3,4)(CR ₂ O)(C ₂ H ₂ O)C ₄ H ₂ CH=CHCOCH ₂ CH ₂ N(CH ₂) ₁ (
3-Ethory-4 methory benzalace-	(we)(confected operations of the confective (CBF) (~			
	(3.4)(C ₂ H ₂ O)(CH ₂ O)C ₃ H ₂ CH=CHCOCH ₂ CH ₃ N(CH ₃) ₃ (-)			
6-Nitropiperonalectione at	(3.4)(6)(CH ₂ O ₂)(NO ₂)C ₄ H ₂ CH=CHCOCH ₂ CH ₂ N(CH ₂) ₂ (-			
6-Nitros eratralacetona #	(3,4,6)(CH ₂ O ₂₄ (NO ₂)C ₄ H ₂ CH=CHCOCH ₂ CH ₂ N(CH ₂) ₄			
	(20-25°C)			
Methyl & naphthyl ketone =	&-Culli-COCH, CH, N(CH,), (70%)			
P-4cecotetralin ti	6-(8-Domethylamanopropropri)-tetralin (—)			
2- Leety lphonont house st	2-(#-Dumethylamanopropeonal)-phenanthrene ()			
3 Seety phenanthrone 45	3-(8-Demethylamunopropount)-phenanthrene ()			
9-1 cetylphenantheans 45	9-(2-Dimethylaminopropostal) phenanthrene (-)			
CYT(Opentanone st	2-(Dimethylaminopropions) phenantarene (-)			
Cycloharanone #	2-(Dimethy Inmandmethy) -(Priobezzantos (83%)			
4-Methylevelohannan at	2 (Demethy laminomethy) + methy les clohezanone (-)			
Alenthone to	Dimethelaminomethylmenthone † (51%)			
a-Tetralone a	6-(Damethy Lamanomethy D-or tetralogo (70%)			
Keto-1,2,3 4-tetrahydro	p-(Digital) included a science (see s)			
Phenanthrene st	I-Keto-2-depethylammomethyl-1,2,3,4-tetrahydrophenan-			
	threne (63°3)			
4-Keto-1,2,3,4 tetrahydro-	Marca (se S)			
phenanthrene H	4-Keto-3-dimethylaminomethyl-1,2,3,4-tettahydrophenan-			
	therae (77%)			
2-Acet offuran sa	2-Furyl &-demethylammorthyl ketone (-)			
urfuralections #	C.H.OCH = CHCOCH, CH, N(CH,), ()			
Acetylchiophera 15 to	2 Thomas S-damethylamunoethal ketone (47%)			
- Acctvidation and broad and	# Themsthatement and 2 debense them ketone (41%) 1			
	(60%) Through the International Control of the Cont			
-Acetyl-I-phony tabus- 1-14	& Denethylamorethyl 4 phenyl 2-thusolyl ketons (!			
	4 Dunethylamunomethylaotepyrane (90%)			
soantspyrine 17	1 Fhenyl 2,5-damethyl-4-damethylaminomethylpyragolooe-3			
toets 1-9-methy learbasofe **	a Dometh demonstral 2-78 methylegridged) ketone (tSC)			
Keto-9-marky 1 2 2	#-Dunethylamanoethyl 3-(9-methylcarbasyl) ketonz (61%) 1			
Jurocarbasole sa	1-Keto-2-demethylamanomethyl-9-methyl-1,2,3,4-tetrahydro- rardarole (10-15%)			
tetaldebyde 18	HCH-b-NCH-b-C(CH-OH)CHO (practically quantitative)			
ropiousldehyde 18	CH*ClCH*N(CH*)*I*CH0 (→) CH*ClCH*N(CH*)*I*CH0 (12½)			

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EXAMPLES OF THE REACTION

Reactants Product (Yield) Butyraldehyde 15 CH₁CH₂CH(CH₂N(CH₁)₂)CHO (—) $CH_1CH_2C(=CH_2)CHO(-)$ Isobutyraldehyde 15 (CH₁)₂C[CH₂N(CH₄)₂]CHO (70-80%) Isovaleraldehyde 15 (CH₁)₂CHCH[CH₂N(CH₄)₂]CHO (--) (CH₄)₂CH(CH₂OH)[CH₂N(CH₄)₂;CHO (—) Hexahydrobenzaldchyde 15 1-Dimethylaminomethylhexahydrobenzaldehyde (-) 2-Methylquinoline 23 2-(\$\beta\$-Dimethylaminoethyl)-quinoline (-) 2-Methyl-4-hydroxyquinoline 25 2-(β-Dimethylaminocthyl)-4-hydroxyquinoline (--) 2-Ethoxy-4-methylquinoline # 2-Ethoxy-4-(β-dimethylaminoethyl)-quinoline (-) Diethylamine, formaldehyde, and 2,4-Dinitrophenylacetie acid 67 (2,4)(NO₂)₂C₆H₄CH[CH₂N(C₂H₄)₂J₂ (52%) Benzylacetoacetic acid 16 CH₂COCH(CH₂C₂H₄)CH₂N(C₂H₄)₂ (46%) Monoethylmalonate 43 C₂H₂OOCCH₂CH₂N(C₂H₂)₂ (21%) C2H2OOCCH[CH2N(C2H2)2)2 (--) Monocthyl methylmalonate 43 C2H4OOCC(=CH2)CH2 (88%) Monoethyl ethylmalonate 42 C2H2OOCC(=CH2)CH2CH3 (63%) Monocthyl allylmalonate 4 C2H1OOCC(=CH2)CH2CH=CH2 (quantitative) Monoethyl benzylmalonate 41 C2H4OOCC(=CH2)CH2C6H4 (73%) Diethyl 2,6-dimethyltetrahydropyrone-3,5-dicarboxylate 25 Diethyl 2.6-dimethyl-3-diethylaminomethyltetrahydropyrone-3.5-dicarboxylate (30%) Phenylacetylene 25 $C_tH_tC \equiv CCH_tN(C_tH_t)_t$ (80%) (2) NO2CeH4C = CCH2N(CeH4): (-) 2-Nitrophenylacetylene 4-Nitrophenylacetylene 25 $(4)NO_{2}C_{2}H_{4}C = CCH_{2}N(C_{2}H_{4})_{2} (--)$ 4-Methoxyphenylacetylene 25 (4)CH₂OC₅H₄C = CCH₂N(C₂H₂)₂ (—) a-Picoline 27 2-(8-Diethylaminoethyl)-pyridine (80%) Quinaldine 7: 27 2-(6-Diethylaminoethyl)-quinoline (33%) Diethylamine hydrochloride, formaldehude, and Acetone 8 CH1COCH2CH2N(C2H5)2 (66%) Acetophenone 10 CtH1COCH2CH2N(CtH1)2 (45%) 2-Nitroacetophenone 12 (2)NO2C6H4COCH2CH2N(C2H5)2 (80-90%) 3-Nitroacetophenone 12 (3) NO₂C₆H₄COCH₂CH₂N(C₂H₅)₂ (80-90%) Acetoveratrone 11 (3,4)(CH₁O) + C₅H₄COCH + CH₂N(C₂H₅) + (--) Benzalacetone 9 $C_6H_5CH=CHCOCH_5CH_5N(C_2H_5)_2$ (60%) 4-Anisalacetone 50 (4)CH₂OC₅H₄CH==CHCOCH₂CH₂N(C₅H₅)₂ (60%) 2-Butoxybenzalacetone 5: $(2)C_1H_2OC_2H_4CH = CHCOCH_2CH_2N(C_2H_3)_2$ (5-10%) Methylenedioxybenzalacetone 9 (3,4)(CH₂O₂)C₂H₂CH=CHCOCH₂CH₂N(C₂H₅)₂ (60%) 3,4-Dimethoxybenzalacetone 9.51 (3,4)(CH₂O)₂C₆H₂CH=CHCOCH₂CH₂N(C₂H₅)₂ (60%) 3-Ethoxy-4-methoxybenzalacetone 51 $(3.4)(C_2H_2O)(CH_2O)C_3H_2CH=CHCOCH_3CH_2N(C_2H_2)_2$ (--) 6-Nitropiperonalacetone 55 (3,4.6)(CH-O-)(NO-)C₆H-CH=CHCOCH-CH₂N(C₂H₃)₂ (50%)6-Nitroveratralacetone 55 $(3,4,6)(CH_4O)_2(NO_2)C_6H_2CH=CHCOCH_2CH_2N(C_2H_5)_2$ (40%)2-Acetylphenanthrene 65 2-(β-Diethylaminopropionyl)-phenanthrene (--) 3-Acetylphenanthrene 63 3-(6-Diethylaminopropionyl)-phenanthrene (--) 9-Acetylphenanthrene 65 9-(β-Diethylaminopropionyl)-phenanthrene (--) 2-Methylcyclopentanone 8 2-Methyl-5-diethylaminomethylcyclopentanone (71%) Cyclobexanone 43 2-Diethylaminomethylcycloheranone (83%) 2-Methylcyclohexanone 8 2-Methyl-6-diethylaminomethylcyclohexanone (60-65%) 1-Keto-1,2,3,4-tetrahydrophenanthrene 15

threne (59%)

1-Keto-2-diethylaminomethyl-1,2,3,4-tetrahydrophenan-

^{*} References 67-74 appear on p. 341.

Reactanta	Product (Yield)	
4-Keto-1,2,3,4-tetrahydrophe-	a a sa a sa	
nanthrens 15	4-Keto-3-daethylaminomethyl-1,2,3,4-tetrahydrophenan- threne (31 %)	
1-Keto-9-methoxy-1,2,3,4-tatra-	1-Keto-2-darthylamssomethyl-0-methoxy-1,2,3,4 tetrahyd	
hydrophenanthrena ²⁰	phenanthrene (41%)	
I-Keto-9-acetoxy-1,2,3,4-letra-	I-Keto-2-derthylamanomethyl-0-acetoxy-1,2,3,4-tetrahydr	
hydrophenanthrena 10	phenanthreen (20%)	
Furfuralacetona 40		
Chromanona 71	3-Diethylaminomethyl 2-thirtyl ketona (39") 6-Diethylaminoethyl 2-thirtyl ketona (40")	
2-Acetylthiophena 18		
2-Acetyldibensothrophena 14	6-Diethylamicomethylantipyrica (—) 4-Diethylamicomethylantipyrica (—)	
Antipyrina 17	4-Dethylamanomethylantipyrana (—) 4-Dethylamanoethyl 2-(9-methylambaryl) hetona (20-25 B-Diethylamanoethyl 2-(9-methylambaryl) hetona (83°;)	
2-Acetyl-9-methylcarbasols **	B-Diethylaminoethyl 3-(9-methylambayi) keiona (83°); B-Diethylaminoethyl 3-(9-methylambayi) keiona ()	
3-Acetyl-9-methylcarbasolo **		
2-Acetyl-4-phenylth:asole 18	g-Disthylamatorings (Clf _b) _g C[Clf _b N(C ₂ lf _b) _a)ClfO (—)	
laobutyraldaby do 18	Contract	
Diethanolamins hydrockloruse, form-	and the same of th	
sidekyde, and 2-Acets liuran **	Dr.p.(f-hydroxyethyl)-aminorthyl 2 buryl ketona ()	
Dipropulamene, formalisekyde, and	CH2COCH(C1R4)CH4N(C1Hr)1 (40%)	
Ethylacetoacetic acid is	CHCOCHCINDCHT	
Durapylamina hydrochlorule, form-		
idehyde, and	(OCH,OC,H,CH=CHCOCH,CH,N(C,H)); (83°;)	
Anisalacetons 10	(6) CH ₂ OC ₂ H ₂ CH arctic 2-furyl hetone (-) p. Dipropylaminorthyl 2-furyl hetone (-)	
2-Acetylfuran to	5-Dipropylaminorthyl 2-myt krone () 5-Dipropylaminorthyl 5-phenyl-2 thanolyl ketone ()	
2. A contulat phone it his sola is	property	
Dibutylamine hydrochloride, for m		
uldskyde, and	g-Dibutylaminorthyl 2 fwyt brione (-) (4)CH ₂)C ₄ H ₂ CH=CHCOCH ₂ CH ₁ N(C ₄ H ₂) ₂ (16 ⁴)	
2-Acety lluran 13	(t)CH/OC/H/CH#CHCOCHCH/MCCHC	
Anisalacetona 50	l ·	
Dissonylamine hydrochlaride,	CHICOCHCHIN (Callada (24%)	
formaldehyde, and Aretophenona ⁶⁶	Chicochical details	
to at the state of the part of		
	Methyldwthyl & (+ hydroxy-2-quaciyi) ethylethylennia-	
2-Methyl-4-hydroxyquinohus	mine (-1	
u-Mahylaminopropusphrame	GHACOCHACHANICHAR R = 4-anupyrylmethyl ()	
hydrochlorule, formaldskyde, and	Chitechtan dentan	
Antipyrine se B-Acetylethyllerstylamine kydro		
B-Acetylethylorasymmetric chloride, formalishyde, and	I-Sentyl-3-(mby-trusynthyl)-4-methyl-4-kythusyyeperi	
Acetone ⁶⁶	diae (→)	
Dibensylamine bydrocklands,	CHOCHOCHCH=CHCOCHCHIN CHCARCI (BUC)	
formalirhyde, and Anisalacetone to	(I Cap cine	
	ill quasi letore not received from the reaction mixture.	

Examples of the Reaction

Reactante Product (Yield) Benzyl-(2-cyclohexanonylmethyl)amine hydrolnomide, formaldehyle, and Acctone 23 2-Benzyl-4-acetyl-10-hydroxydecahydroisoquinoline (73%) Acetophenone 35 2-Benzyl-4-benzoyl-10-hydroxydecahydroisoquinoline (7.5%) 3,4-Methylenedioxybensyl-(2-cyclo-Lexanonylmethyl)-amine hydrotromide, formaldehyde, and Acetone 33 2-(3,4-Methylenedioxybenzyl)-4-acetyl-10-hydroxydeenhydroi-oquinoline (--) Methylandline, formaldehyde, and Quinaldine hydrochloride? 2-(β-Phenylmethylaminoethyl)-quineline (-) Methylandline hydrochloride. formaldehyde, and Antipyrine 17 4-(Phenylmethylaminomethyl)-antipyrine (49%) Piperidine, formaldehyde, and Antipyrine 6 4-Piperidinomethylantipyrine (44%) Cyclohexanone \$ 2-Piperidinomethyleyclohexanone (37%) 4-Nitrophenylacetic acid @ (4) NO₂C₆H₆CH(COOH)CH₂NC₅H₁₆ (64%) 2,4-Dinitrophenylacetic acid C (2,4)(NO₂)₂C₂H₂CH(CH₂NC₃H₁₀)₂ (41%) 2-Nitromandelic acid 67 (2) NO₂C₄H₄C(OH)(COOH)CH₂NC₄H₁₂ (75%) Renzovlacetic acid & CtH1COCH1CH1NCtH10 (90%) Pyruvic acid = CallieNCH-CHCOCOOCH: † (43%) Methylacetoacetic acid & CH1COCH(CH2)CH2NC2H19 (60%) Ethylacetoscetic acid 33 CH2COCH(C2H2)CH2NC2H10 † (--) Allylacetoacetic acid 24 CH-COCH(CH-CH=CH2)CH-NC4H12 (30-45%) Benzylaretoacetic acid 2 CH2COCH(CH2C4H2)CH2NC3H29 (46%) Levulinic acid 23 CH2(CH2NC4H10)COCH2CH2COOH (48%) † Benzylmalonic acid 13 CtHtCHtC(COOH)tCHtNCtHtn (85%) Tartronic acid 42 C(OH)(COOH) CH NC H10 (14%) Diethyl 2,6-dimethyltetrahydropyrone-3,5-dicarboxylate 25 Diethyl 2,6-dimethyl-3-(piperidinomethyl)-tetrahydropyrone-3.5-dicarboxylate (73%) Phenylacetylene $C_tH_tC \equiv CCH_tNC_tH_{10}$ (--) 4-Methoxyphenylacetylene $(4)CH_{2}OC_{2}H_{4}C \equiv CCH_{2}NC_{3}H_{10} (--)$ 4-Acetylaminophenol 21 2-Piperidinomethyl-1-acetylaminophenol (--) B-Naphthol = Piperidinomethyl-8-naphthol (-) 8-Hydroxyquinoline 21 Piperidinomethyl-S-hydroxyquinoline (-) Quinaldine hydrochloride? 2-(8-Piperidinoethyl)-quinoline (72%) Indole 74 3-Piperidinomethylindole (--) Piperidine hydrochloride, formaldehyde, and Acetone C CH1COCH2CH2NC3H10 (good) Methyl ethyl betone @ CH2COCH(CH2)CH2NC5H10 (--) Pinacoline @ (CH₂)₂CCOCH₂CH₂NC₂H₁₂ (—) Allylacetone ** CH = CHCH CH COCH CH NC H10 (20%) $CH_2 = CHCH_2CH(CH_2NC_2H_{10})COCH_2$ (—) Acetophenone 11 C,H;COCH-CH-NC;H19 (90%) (2)NO₂C₂H₄COCH₂CH₂NC₃H₁₀ (80-90%) 2-Nitroacetophenone 12

(3)NO₂C₂H₄COCH₂CH₂NC₂H₁₂ (89-90%)

(4)CH₂OC₂H₄COCH₂CH₂NC₂H₂, (--)

3-Nitrozoetophenone 12 Acetoanisone 11

^{*} References 67-74 appear on p. 341. † In this instance the amine hydrochloride was used.

TABLE V .—Continued

Reactants	Product (Yield)
	C ₄ H ₂ COCH(C ₄ H ₄)CH ₄ NC ₅ H ₁₀ ()
Desosybensoin 11	
Acetoverstrone It	
Beosslacetone : 42 kg	
2-Methoxybensalacetone	
2-Ethoxybenzalacetone as	
2-Proposybenzalecetone	
2-Butoxybensalacetees #4	(2)CallaOCallaCH=CHCOCHaCHaNCallas (60%) (4)CHaOCallaCH=CHCOCHaCHaNCallas (60%)
Anuslaceione * M	(4) CH ₂ OC ₄ H ₂ CH ² CH ² CHCOCH ₂ CH ₂ NC ₃ H ₃ NC ₃ H
Piperonalacetene #- #1	
3,4-Dimethoxy bensaleretone # #1	(3,4)(CH ₂ O) ₂ C ₄ H ₂ CH ₂ CH ₂ CH ₂ CH ₂ NC ₆ H ₁₍₀ ()
Ethyl 4 anseyl ketone !!	(e)Chipochites and (in (a)
3 Methoxy-4-ethoxybensalece- tone #1	(3,4)(CH ₁ O)(C ₃ H ₆ O)C ₆ H ₄ CH=CHCOCH ₅ CH ₅ CH ₇ NC ₅ H ₁₆ ()
3-Ethory-4-methoxybenzalace-	(3,4)(C ₃ H ₂ O)(CH ₃ O)C ₃ H ₂ CH=CHCOCH ₃ CH ₃ NC ₃ H ₁₀ ()
tone 41	(3,4)(C ₃ H ₂ O)(CH ₂ O)C ₄ H ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ NC ₄ H ₁₀ (3,4,6)(CH ₂ O ₃)(NO ₃)C ₄ H ₂ CH ₂ CH ₂ CH ₂ CH ₂ NC ₄ H ₁₀
6-Nitiopiperonaliscetone #8	(3,4,8)(C112-3)(1/O)/O)/O
	(69-65%) (3,4,6)(CII ₂ O) ₂ (NO ₂)C ₄ II ₄ CII=CIICOCII ₂ CII ₄ NC ₄ II ₁₄
6-Nitroverstrelacetone #6	(3,4,6)(CH2O)(CO) CI-CO
2-Acctylphonenthrone 44	3-(\$-Paperidinopropionyl)-phenauthrono ()
8-Acetylphenenthrone 65	
9-Acetylphenenthrene **	
Methyl # nephthyl ketone #5	
β-Acetotetrelin !!	
Cyclopentenone #	2-Piperidinametayiryetahaxaqısın (62%) 2-Piperidinametayiryetahaxaqısın (62%)
Cyclohexenone 46	
4-Methyloyelolisaanone 48	g-Paperisinomethyl-a-tetralena (75%)
a-Tetralone #	pre special contract of the second contract o
1-Keto-1,2,3,4-tetishydio- phenenthiene 18	1-Keto-2-piperkinomenkyi-1,4,3,4-tetrohydraphunan- throne ()
	and the state of t
4-Keto-1,2,3,4-totrehydro-	4-Kato-2-phostilinomethyl-1,2,4,4-tettaliyih iildicaali
phonanthi eno 10	thress () I-keio-3-piperidino-9-methoxy-1, 2, 4 telighyd spheisanthre
	I-Arto-3-piperidino-9-methody-1,27-1
1-Kete-0-methoxy-1,2,3,4-1stra-	(63°)
bydrophenenthrone ¹⁰ 2-Acetylfuren 1 ³	(63%) # Piperblincethyl 2 furyl ketene () # Piperblincethyl 2 furyl ketene ()
Fulluralacetons 48	C.H.OCH -CIRXK HK HATTER
2-Acetylthinphens 10, 15	
2-Acetykhbennahlaphana 14	
4-Acetylchameothiophene 13	p-Piperidinceth ye about 2 this ply beings (-)
2-Acetyl-4-phenylthlasole 18	A Piperklinostnyi v passay to 270113
Antipyrine 5, 17	4-Piperidinomethylastipytim (***) 2-Piperidinomethyl-4-chromome (2***) 2-Piperidinomethyl-4-chromome (2***)
Chromanone 71	3-Piperidiament, Mightight (~) (Cliph ClClis Mightight (A)
Isobutyraldeliyda 18	(CH ₂) ₂ C(CH ₂ NC ₂ H ₂)C(H ₂)C(H ₂) (CH ₂) ₂ C(HCHCH ₂ NC ₂ H ₂)C(H ₂)C(H ₂ (CH ₂)C(H ₂)C
Isovale, aldebyde II	(CHa5c HCH(CH4NC)Hab(H1) (-) (CHa5cHC CH4OHH(CH4NC)Hhb(CH4)(H1) (-) 1-Tpoti-Broweshytheanhydrol oran Molyyda)
Heranydroken saldelty-la 18	1-Liber planeting and a
Tetrahudroisoovinulina hulra-	to a standard (cel
thlorple, formalishple, an I	3 (8 (tempoplethyl) 1,2,7,4 setralicalism principles ().
Acetophenone II 2-Acetylphenonthuene 14	3 (5 (tomorphothyl)-1,2,7,4 set; shiphindon printed in a 2 2 2 1,2,1,4 Totachydraino-painedin 20 (1) (1) (1) (1) (1) (1)

Reactants	Product (Yiekl)
3-Acetylphenanthrene (5	3-(\$-1,2,3,4-Tetrahydroisoquinolinopropionyl)-phenanthrene
9-Acetylphenanthrene 65	0-(β-1,2,3,4-Tetrahydroisoquinolinopripionyl)-phenanthrene
Cyclohexanone 40	2-(1,2,3,4-Tetrahydroisoquinolinomethyl)-cyclohexanone ()
a-Tetralone 16	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydronaphthalene (66%)
1-Keto-6-methoxy-1,2,3,4-tetra-	
hydronaphthalene 16	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-6-methoxy- 1,2,3,4-tetrahydronnphthalene (63%)
1-Keto-6-acetoxy-1,2,3,4-tetra-	
hydronaphthaleno 16	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-6-acetoxy- 1,2,3,4-tetrahydronaphthalene (81%)
1-Keto-7-methoxy-1,2,3,4-tetra-	
hydronaphthaleno 16	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-7-methoxy- 1,2,3,4-tetrahydronaphthalene (76%)
1-Keto-7-acetoxy-1,2,3,4-tetra-	
hydronaphthaleno 16	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-7-acetoxy- 1,2,3,4-tetrahydronaphthalene (61%)
1-Keto-1,2,3,4-tetrahydrophen-	
anthrene 15	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetra- hydropheaanthrene (61%)
4-Keto-1,2,3,4-tetrahydrophen-	
anthrene 15	4-Keto-3-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetra- hydrophenanthreae (34%)
1-Keto-9-methoxy-1,2,3,4-tetra-	
hydropheaanthrene 70	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-9-methoxy- 1,2,3,4-tetrahydrophenanthrene (46%)
1-Keto-9-acetoxy-1,2,3,4-tetra-	
hydrophenanthrene 70	1-Keto-2-(1,2,3,4-tetrahydrois oquinolinomethyl)-9-acetoxy- 1,2,3,4-tetrahydrophenanthrene (72%)
2-Acetyldibenzothiophene 14	β-(1,2,3,4-Tetrahydroisoquinolino)-ethyl 2-dibenzothicnyl ketone (30%)
2-Acetyl-9-methylcarbazole 69	β-(1,2,3,4-Tetrahydroisoquinolino)-ethyl 2-(9-methylearhazyl) ketone (37%)
3-Acetyl-9-methylcarbazole 65	β-(1,2,3,4-Tetrahydroisoquinolino)-ethyl 3-(9-methylcarhazyl) ketone (78%)
6-Methoxy-1,2,3,4-tetrahydroiso-	
quinoline hydrochloride, formalde-	
hyde, and a-Tetralone 16	1 V-1-0/6 C
	1-Keto-2-(6-metnoxy-1,2,3,4-tetrahydroisoquinolinomethyl)- 1,2,3,4-tetrahydronaphthalene (68%)
1-Keto-6-methoxy-1,2,3,4-tetra- hydronaphthalene 16	1 Vote 2 (6 math - 1 2 2 4 / 1 2 2 4 / 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)- 6-methoxy-1,2,3,4-tetrahydronaphthalene (88%)
1-Keto-6-acetoxy-1,2,3,4-tetra- hydronaphthalene 16	1. Wate 9 (6 mathems 1 9 2 4 4 4 - 1 - 1 4 4 4 4 4 1 1 1 1 1 1 1 1
ny dronaphtnatene **	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)- 6-acetoxy-1,2,3,4-tetrahydronaphthalene (74%)
1-Keto-7-methoxy-1,2,3,4-tetra-	o-actiony-1,2,0,4-tetranydronaphthaiene (14%)
hydronaphthalene 16	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-
	7-methoxy-1,2,3,4-tetrahydronaphthalene (68%)

^{*} References 67-74 appear on p. 341.

TUBLE V-Continued

Reactants	Product (Yield)		
1-Keto-7-acetoay-1.2.3.4-tetra-	- Lander of the Company of the Compa		
hydronephthalene 1*	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl) 7-acetoxy-1,2,3,4-tetrahydronophthalens (64°)		
forpholine, formalishyde, and Phenol #	2,4,8-Tri-(morpholanomethyl)-phenol ()		
lorpholine hydrachtoride, formal-			
chyde, and	8-Morpholinoethyl methyl ketone (73%)		
Acetone o	e-(Morpholmorethyl)-ethyl ethyl ketone (50%)		
Diethyl ketone 4			
Acetophenone et			
Acetoverstrone @			
2-Acetylphenanthrene 71			
3-Acetylphenanthrens 71			
Cyclopentanone 47			
Cyclohexanone #			
2-Methylcyclohezanone 47 4-Methylcyclohezanone 47			
e-Nethylcyclonexanous ~			
5.5-Dimethory-hydrindose	2-Morpholanomethyl-5.6-damethysyl-hydrandone (37%)		
1-Keto-1.2.3.4-tetrahydrophen-			
Anthrene 71	1-Keto-2-morphohaemethyl-1,2,3,4-tetrahydrophenanthrene (41%)		
4-Keto-1,2,3,4-tetrahydrophen- anthrene 73	3. Morpholacomethyl-4-keto-1,2,3,4-tetrahydrophenanthrene		
2-Acetylthiophene 47			
Antipyrine 47	4-Morpholanomethyl-4-chromanone (37%)		
Chromanose 71	- Constant		
Piperanne hydrochlorule, formalde-	p ->		
yde, and	N,N'-Da-(5-bensoylethyl)-paperanne (—) N,N'-Da-(5-bensoylethyl) paperanne (—)		
Acetophenone 11	N.N'-Dr-(5-4 methoxybensoyiethyl) -pipersune (—) N.N'-Dr-(5-3,4-dimethoxybensoyiethyl) -pipersune (—)		
Acetoanisone 11 Acetoverstrone 11	N.NDr-(6-3,4-disards-xysenio)4cH2COOH)CH2CH3 †		
Malone acid 10	(HOOC) CHCHEROLOGICAL		
pratome acid	HOOCCH,CH,NCH,CH,N(CH,CH,COOH)CH,CH, (19%)		
	N.N'-Dr-(antipyrylmethyl)-superanne ()		
Antipyrine 17	N,N-D-quinger-		

⁸⁷ Mannich and Stein, Ber., \$8, 2659 (1925).

⁴ Blicke and Maxwell, J. Am. Chem. Soc., 64, 428 (1942).

^{**} Ruberg and Small, J. Am. Chem. Soc., 60, 1591 (1938). re Burger, J. Am. Chem. Soc., 60, 1533 (1938). Burger, J. Am. Carm. and Lions, J. Proc. Roy. Soc. N. S. Wales, 72, 273 (1938)
B Harradonce, Hughes, and Lions, J. Proc. Roy. Soc. N. S. Wales, 72, 273 (1938)

[&]quot;Harradence, Hugnes, and Burger, J. Am. Chem. Soc., 60, 2464 (1938).

Mosettig, Shaver, and Marian, Roy. Soc. N. S. Woles, 72, 234 (1938).
 Harradence and Lions, J. Proc. Roy. Soc. N. S. Woles, 72, 234 (1938).

¹⁴ Kuhn and Stein, Ber., 70, 567 (1937).

Nabn and Stein, Pita Stewart, J. Am. Chem. Soc., 65, 200 (1944).

CHAPTER 11

THE FRIES REACTION

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INTRODUCTION

The Fries reaction consists in the conversion of an ester of a phenol to an o- or p-hydroxyketone, or a mixture of both, by treatment with aluminum chloride.

$$\begin{array}{c|c}
\text{OCOR} & \text{OH} & \text{OH} \\
\hline
& & \text{COR} \\
& & \text{COR}
\end{array}$$

A second method available for the synthesis of similar compounds is the Friedel-Crafts reaction, in which a phenol, or an ether of a phenol, is condensed with an acid chloride or acid anhydride in the presence of aluminum chloride. In spite of the fact that the Fries reaction requires two steps—the preparation of the ester and the rearrangement to the hydroxyketone—as compared to the single step in the Friedel-Crafts synthesis, the Fries method usually is to be preferred for the preparation of phenolic ketones. The yields are ordinarily better and the experimental procedure does not have to be modified greatly to adapt it to a variety of esters.

Three different mechanisms for the Fries rearrangement have received serious consideration. In one of them the ester is assumed to react with aluminum chloride to give an acid chloride and a phenoxyaluminum chloride which combine to form a derivative of the hydroxyketone.

$$\begin{array}{c} \text{OCOR} \\ & \longrightarrow \\ + \text{AlCl}_2 \rightarrow \\ & \longrightarrow \\ + \text{RCOCI} \\ & \rightarrow \\ + \text{RCOCI} \rightarrow \\ +$$

In another scheme, it is proposed that one molecule of the phenyl ester is acylated by another molecule

$$\begin{array}{c}
OCOR & OCOR & OH & OCOR \\
OCOR & OCOR & OH & OCOR \\
OH & OCOR & OH & OCOR \\
OH & OCOR & OH & OCOR \\
OH & OCOR & OH & OCOR \\
OH & OCOR & OH & OCOR \\
OH & OCOR & OH & OCOR \\
OH & OCOR & OCOR & OH & OCOR \\
OH & OCOR & OCOR & OH & OCOR \\
OH & OCOR & OCOR & OCOR & OCOR \\
OH & OCOR & OCOR & OCOR & OCOR & OCOR \\
OH & OCOR & OCOR & OCOR & OCOR & OCOR & OCOR \\
OH & OCOR &$$

In the third mechanism, the Fries reaction is considered to be a true intramolecular rearrangement in which the acyl group shifts directly from the oxygen atom to the carbon atom of the ring

Certain experimental facts can be cited to support each of these mechanisms, but it has not yet been possible to prove or disprove any one of them.

Blatt, Chem. Rev., 27, 429 (1940).

Esters of haloacetic acids and of alkyl, alkoxyl, and halosen-substituted aromatic acids have been employed. Esters of purely sliphstic unsaturated acids appear not to have been tried, but certain eters of cinnamic acid have been found to rearrange.

Rosenmund and Schnurr 3 studied the relative rates at which the Fries reaction takes place with different esters of the same phenol (thymol). Their observations are summarized in the following list, in which the styl groups are arranged in the order of decreasing rate of reaction.

$$C_{\epsilon}H_{2c+1}CO \ (n=1 \ to \ 5) > C_{\epsilon}H_{5}CH_{2}CO > C_{\epsilon}H_{5}CH_{2}CH_{2}CO > C_{\epsilon}H_{5}CH_{2}CO > C_{\epsilon}H_{5}CH_{2}CO > C_{\epsilon}H_{5}CH_{2}CO > C_{\epsilon}H_{5}CO$$

is an example of the magnitude of the differences in rate, it may be noted is after five hours in nitrobenzene solution at 20° the rearrangement of thymyl acetate was 60% complete and that of thymyl benzoate only 4% The order of reactivity of the acyl groups is the same for rearrangement to either the o- or p-hydroxyketone.

The stability of esters containing the less reactive acyl groups somelimits the usefulness of the Fries rearrangement. For example, the benzoate of α-naphthol does not undergo a Fries reaction at the the Delicotte reaction at the crimery temperature. 12 The butyrate of α-naphthol furnishes, after examely to eighteen hours at 0°, 35% of 4-butyryl-1-naphthol and State of 2-butyryl-1-naphthol. At 100-120°, the same ester furnishes 5. of 1-butyryl-1-naphthol, 55% of 2-butyryl-1-naphthol, and 2% of 5. of 1-butyryl-1-naphthol 12 adibutyryl-1-naphthol.13

$$OH COR + OH COR - OCOR OH COF$$

The rearrangement of p-cresyl cinnamate does not take place at temper-The residue that at which the ester undergoes decomposition.

With the aliphatic esters of certain phonols, an increase in the size of Win the group favors the formation of o-hydroxyketone. This is parits says before This is parameter of the aliphatic acid esters of m-cresol, for only the acetate converted to a p-hydroxyketone. be converted to a p-hydroxyketone. The same tendency, although be connected, has been observed with aliphatic acid esters of α - β pronounced, has been observed with aliphatic acid esters of α -Promote As indicated by the examples just cited, the importance of the acyl radical in determining the is the next radical in determining the course of the rearrangement is no the structure of the phenolic radical in the structure of the phenolic radical in the structure of the phenolic radical in the structure of the phenolic radical in the structure of the phenolic radical in the structure of the phenolic radical in the structure of the phenolic radical in the structure of the phenolic radical in the structure of the phenolic radical in the structure of the phenolic radical in the structure of the phenolic radical in the structure of the structure of the phenolic radical in the structure of the structure of the phenolic radical in the structure of the structur on the structure of the phenolic residuc. Although it is probable to state that an increase in the correct to state that an increase in the size of the acyl group of a J. prakt. Chem., [2] 135, 49 (1932).

: Ice J. Am. Chem. Soc., 57, 202 (1935).

particular ester will increase the tendency toward formation of the ohydroxyketone, it is still possible to prepare p-hydroxyketones containing very large acyl groups. Phenyl palmitate and phenyl stearate, it is for example, furnish the p-hydroxyketones (197%, 21%) when the reaction is carried out by heating the esters to 70° with aluminum chloride in tetrachloroethane. The yield of p-hydroxyketone from phenyl palmitate is less than half that from phenyl captylate but the ratio of para- to ortho-hydroxyketones is not greatly different with these two esters (1.32 to 1.35).19

Structure of the Phenoxyl Group

The structure of the phenolic portion of the ester is the factor of greatest importance in determining whether a Fries reaction will take place and whether the product will consist principally of the o-or p-hydrocyketone. The importance of this factor is revealed by examination of the products from esters of monosubstituted phenols. The presence of a products from esters of monosubstituted phenols. The presence of a mada-directing group on the aromatic portion of the phenyl ester usually interferes with the Fries reaction. For example, the reaction does not occur if the phenolic residue carries a nitro or benoyl group in either the orthor or part position; the presence of an acetyl or carboxyl group in the orthor position hinders the reaction, and, in the para position, prevents

If the phenyl ester contains a single alkyl group in the phenolic ring, then the position of this substituent has a profound influence on the nature of the product. For example, esters of o-cresol yield predominantly o-hydroxyketones, and esters of pressol yield redominantly o-hydroxyketones, and esters of pressol yield exclusively o-hydroxyketones, and esters of pressol yield exclusively o-hydroxyketones, the effect of a para substituent has been observed with a variety of alkyl groups and with halogen; the effect of orthos substituent has been observed with several alkyl group; the effect of a meta substituent has been determined only with esters of m-cresol

The rearrangement products of more than fifty disubstituted phenol esters are shown in Part C of the tabular survey of the Fries reaction (p. 369). It will be noticed that with three cates, 2,6-dimethylphenyl acetate, 2-ethyl-5-methylphenyl acetate, and 2-methyl-6-ethylphenyl acetate, products formed by migration of an alkyl group were isolated. It is probable that these migrations were the result of the use of high temperatures and prolonged reaction times and that they would not occur if more gentle experimental conditions were used. Thus, the carrivaryl and thymyl esters yielded the expected p-hydro-tyketones without migration of alkyl groups when mild experimental procedures were used.

¹⁴ Bell and Driver, J. Chem. Soc., 835 (1940).

APPLICABILITY AND LIMITATIONS

The structure of the phenyl ester determines whether or not a Fries reaction will take place. If the reaction does occur with a particular ester, the product may be either the o- or p-hydroxyketone or a mixture of the two. The nature of the product is influenced not only by the structure of the ester, but also by the temperature, the solvent, and the amount of aluminum chloride used. By variation of these last three factors it is often possible to direct the course of the reaction so that either of the isomeric ketones may be the major product from the same ester. Since it is usually possible to separate the two ketones, the synthesis is often useful even when it cannot be directed to the exclusive production of one isomer.

Temperature

A temperature effect in the Fries reaction has been observed by many workers.² A striking example has been reported by Rosenmund and Schnurr,³ who found that at 25° only the p-hydroxyketone (80%) was obtained from m-cresyl acetate and aluminum chloride, while at 165° only the o-hydroxyketone (95%) was formed.

$$\begin{array}{c|c}
OH & OCOCH_3 & OH \\
\hline
CH_3 & \stackrel{25^{\circ}}{\text{AlCl}_2} & \bigcirc CH_3 & \stackrel{165^{\circ}}{\text{AlCl}_2} & CH_2CO \\
\hline
COCH_2 & & & & & & & & & & & \\
\end{array}$$

Similar observations were made in the rearrangement of m-cresyl benzoate; below 100° only the p-hydroxyketone (60%) was formed, and at 175° the ortho isomer was the sole product (95%).

It is not always possible to obtain at will either of the two possible products simply by varying the reaction temperature. For example, the higher aliphatic esters of m-cresol yield the o-hydroxyketones even at low temperatures,⁴ and the esters of o-cresol yield p-hydroxyketones as the principal products even at high temperatures.³ Generally, however, low reaction temperatures favor the formation of the p-hydroxyketones, and if these are desired it is good practice to keep the reaction temperature at 60° or less.³

- ² Eykmann, Chem. Weekblad, 1, 453 (1904).
- ² Rosenmund and Schnurr, Ann., 460, 56 (1928).
- Baltzly and Bass, J. Am. Chem. Soc., 55, 4292 (1933).

Solvents

The Fries reaction can be carried out in the absence of a solvent, but the temperature at which the reaction proceeds at a useful rate is lowered by the presence of nitrobenzene.* * No data are available to show whether the other solvents which have been employed, such as tetrachloroethane and chlorobenzene, also evert this influence. Carbon disulfide has been used in the Fries reaction in a rather special way; the reaction is begun in this solvent, the carbon disulfide then removed by distillation, and the reaction is completed by heating in the absence of a solvent. . There is little information at present concerning the effect of different solvents on the ratio in which the two isomers are produced. However, it has been shown that, in the rearrangement of phenyl caprylate at 70°, the proportion of the p-hydroxyketone formed in nitrobenzene is higher than in tetrachloroethane (71% as compared to 63%).18

Ratio of Ester to Reagent

The aluminum chloride and the phenyl ester are generally employed in approximately equimolar quantities. However, in the rearrangement of gualacol acetate, two moles of aluminum chloride are required." The suggestion has been made that one mole of aluminum chloride is used by complex formation with the alkoxyl group. It would be desirable to have information on the effect of using two moles of aluminum chloride per mole of ester with other, similarly constituted esters, for example the acetate of resortinol monomethyl ether. It has been found that the proportion of p-hydroxyketone produced by rearrangement of phenyl appylate in the presence of two moles of aluminum chloride is higher (63% para, 30% ortho) than that in experiments in which only one mole ov/10 para, 30% ortho) than thus the experimental in the mole of the reagent is used (45% para, 33.5% ortho). It should be noted that the increase in yield of the p-hydroxyketone is at the expense of unreacted material, not at the expense of o-hydroxyketone.

Structure of the Acyl Radical

The acyl radical of the phenyl ester may be either aliphatic or aro-The acyl radical of the purchyl each may be steader anymatic or aromatic. Esters of aliphatic acids as large as steader acid have been used

- Barch, J. Am. Chem. Soc., 57, 2330 (1935). Blicke and Weinkauff, J. Am. Chem. Soc., 54, 339 (1932).
- Wojahn, Arch. Pharm., 271, 417 (1933).
- Cox, J. Am. Chem. Noc. 82, 352 (1939).

 Fieser and Bradsher, J. Am. Chem. Soc. 88, 1739, 2337 (1936). rieser and Bradsher, J. Am. Coers. and., and 1436, 2337 (193).

 Ralston, McCorkle, and Bauer, J. Org. Chem. 5, 645 (1940). -- Raiston, McCorkle, and Paper, J. 172, Cacon, 9, 040 (1940).

 11 Coulthard, Marshall, and Pyman, J. Chem. Soc., 280 (1930).

Again, 2-methyl-6-ethylphenyl acetate yielded 50% of the normal product together with some rearrangement product when the reaction mixture was heated for five hours. When more gentle conditions were employed the yield of the normal product rose to 73% and no rearranged product was reported. In many of the esters the acyl group migrated to the ortho position even though the para position was vacant. This is due in part to the presence of alkyl groups in the meta positions. Apparently, it is also due in part to the high temperatures used, since the esters of carvacrol and thymol furnished the p-hydroxyketones under the mild conditions employed in their rearrangement.

In Part D of the tabular survey of the Fries reaction are given the products obtained from the acetates of seven trialkylphenols, each of which has at least one vacant ortho or para position. In the second experiment, the only product isolated was one involving migration of an alkyl group, and only in the first and seventh were such products entirely absent. In the third experiment the transfer of a methyl group from one molecule to another also occurred. A comparison of the data of Part D of the tabular survey with those of Part C indicates that migrations of alkyl groups occur the more readily as the number of such groups is increased. However, even with the heavily alkylated phenyl esters it is probable that these migrations result from the drastic treatment with aluminum chloride and that they are not an integral part of the Fries reaction.

¹⁴ Auwers, Bundesmann, and Wieners, Ann., 447, 162 (1926).

¹¹ Auwers and Mauss, Ann., 450, 240 (1925).

¹⁷ Auwers and Janesen, Ann., 483, 44 (1936).

The migration or removal of an alkyl group sometimes permits the Fries reaction to occur even with esters of 2.4.6-trialkylphenols. However, since very drastic conditions are required, these forced reactions must be investigated in each individual instance before they can be relied upon for preparative purposes. Part D of the tabular survey of the Fries reaction shows the products obtained from the 2,4,6-trialkylphenols.

The esters of the three dihydroxybenzenes, catechol, resorcinol, and hydroquinone, undergo the Fries reaction. Esters of catechol yield predominantly 4-acyleatechols and secondarily 3-acyleatechols.

The usual technique may be employed with these esters, but it is preferable to treat an equimolar mixture of a diester and catechol with aluminum chloride. 15, 15 Resorcinol esters can be converted to 4-acylresorcinols or to 4,6-diacylresorcinols using a variety of techniques, 20, 21, 22 but 4-acylresorcinols am so readily obtained directly from resorcinol and the acids or acid chlorides that the Fries reaction is seldom used for their preparation.23, 24

The Fries rearrangement of the acetate of 4-acetylresorcinol furnishes the 2,4- (58%) and the 4,6-diacylresorcinol (42%). The formation of the 1,2,3,4-tetrasubstituted derivative is explained as a consequence of chelation which stabilizes the Kekule form leading to the 2,4-diacyl compound.25

Rosenmund and Lohfert, Ber., 61, 2601 (1928). ¹⁹ Miller, Hartung, Rock, and Crowley, J. Am. Chem. Soc., 60, 7 (1938).

¹⁹ Klarmann, J. Am. Chem Soc., 45, 2358 (1926).

¹¹ Rosenmund and Schuls, Arch. Pharm . 265, 308 (1927). Rosenmund, Buchwald, and Debgramms, Arch. Pharm, 271, 342 (1933).

¹¹ Cooper, Org. Syntheses, 21, 163 (1941). 14 Cox. Rec. trav. chim . 50, 848 (1931).

¹¹ Baker, J. Chem. Soc., 1684 (1934).

Aeyl derivatives of α -resoreyelic acid (3,5-dihydroxybenzoic acid) are reported not to give the Fries reaction.²⁶

The acetate of guaiacol furnishes three products in the Fries reaction.²⁷ Particularly to be noted is the presence of a m-hydroxyketone among the products, for the formation of m-hydroxyketones in the Fries reaction is exceedingly rare.

OCOCH₃ OH OCH₃ + CH₃CO OH OCH₃ + CH₃CO OCH₃ + CH₃CO OCH₃
$$+$$
 CH₃CO OCH₃ $+$ CH₃CO OCH

The Friedel-Crafts reaction with guaiacol and acetyl chloride furnishes the same three products, making it evident that the formation of the m-hydroxyketone is related to the ortho methoxyl group and is not a peculiarity of the Fries reaction. The resorcinol derivative yields an o- and a p-hydroxyketone (12%, 11%) but no m-hydroxyketone.²⁶

$$OCOCH^{3} \rightarrow OCOCH^{3} + CH^{3}COOCH^{3}$$

Esters of pyrogallol,²⁸ phloroglucinol,^{28, 29, 30} 1,2,4-trihydroxybenzene,³⁰ and of a number of hydroxydimethoxybenzenes and dihydroxymethoxybenzenes have been studied. The products obtained from these esters are, with few exceptions, those to be expected and the yields are usually quite small. The use of more than one mole of aluminum chloride per mole of the ester might give better results. It has been reported that 2,6-dimethoxyphenyl acetate, with zinc chloride at room temperature in acetyl chloride as the solvent, furnishes the unsymmetrical product, the acetyl group taking a meta position.³¹ The same ester on treatment with aluminum chloride yields the p-hydroxyketone.³²

²⁶ Mauthner, J. prakt. Chem., [2] 136, 205 (1933).

²⁷ Reichstein, Helv. Chim. Acta, 10, 392 (1927).

²⁶ Heller, Ber., 45, 2389 (1912).

²⁹ Heller, Ber., 42, 2736 (1909).

³⁰ Mauthner, J. prakt. Chem., [2] 139, 293 (1934).

²¹ Mauthner, J. prakt. Chem., [2] 118, 314 (1928).

²² Mauthner, J. prakt. Chem., [2] 121, 255 (1929).

The diacetate of 2-methoxy-1,4-dihydroxybenzene undergoes a Fries reaction and vields the dihydroxyketone (38%).*

Esters of a-naphthol furnish 4-acylnaphthols at low temperatures.12, 13, 12 With an increase in the size of the acyl group, the rate of formation of the 4-acylnaphthols falls off to such an extent that the method is of little value for their preparation. Increasing the temperature results in the formation of 2-acytnaphthols and 2,4-diacylnaphthols, β-Naphthyl acetate furnishes I-acetyl-2-naphthol (33-40%) together with 6-acetyl-2-naphthol (5%).22. 24. 25

In the phenanthrene series the Fries reaction offers no advantage over the Friedel-Crafts method for it either leads to difficultly separable or inseparable mixtures (2-acetoxy- and 3-acetoxyphenanthrene) or furnishes the same products as the Friedel-Crafts reaction hut in no better yields (9-acetoxyphenanthrene).36

With one interesting exception, the directive influence of the phenyl group in esters of the hydroxybiphenyls is similar to that of the methyl group in esters of the cresols. Thus, esters of 2-hydroxybiphenyl furoish 3-acyl- and 5-acyl-2-hydroxybiphenyls, 17 the yield of the former increasing with the size of the acyl group.** Esters of 3-hydrocybiphenyl furnish 4-acyl-3-hydroxybiphenyls.33 However, with esters of 4-hydroxybiphenyls the acyl group migrates to the para position of the second benzene ring, yielding 4'-acyl-1-hydroxybiphenyls as well as the expected 3-acyl-4-hydroxyhiphenyls. 4. 9. 29. 40

¹¹ Witt and Braun, Ber., 47, 3216 (1914).

⁴ Fries, Ber., 54, 709 (1921).

¹⁴ Fries and Schimmeischmidt, Ber., \$5, 2935 (1925). Mosettig and Hurger, J. Am. Chem. Soc., \$5, 2931 (1933).

Auwers and Wittig, J. probl. Chem., [2] 103, 99 (1924). H Harris and Christiansen, J. Am. Pharms. Assoc., 23, 530 (1934).

[&]quot; Hey and Jackson, J. Chem. Soc., 802 (1936). " Cheetham and Hev. J. Chem. Soc., 7:0 (1937)-

With the acetate of 4-hydroxybiphenyl the 4-hydroxy-3-ketone is the principal product; with the benzoate the 4-hydroxy-4'-ketone is the principal product.

The Fries reaction of esters of hydroxycoumarins proceeds normally to yield the o-hydroxyketones.^{41, 42, 43, 44} The reaction with the acyl derivatives of 4-methyl-7-hydroxycoumarin, made from resorcinol and acetoacetic ester, provides a synthesis of 2-acylresorcinols.⁴⁵

Although esters of hydroxycoumarins rearrange readily, attempts to carry out the Fries reaction with acetates of the following hydroxychromanones have been unsuccessful.⁴⁵

- 11 Desai and Hamid, C. A., 32, 1254 (1938).
- Limaye, Ber., 67, 12 (1934).
- Limaye and Munje, C. A., 32, 2096 (1938).
- "Sethna, Shah, and Shah, C. A., 32, 549 (1938).
- 45 Russell and Frye, Org. Syntheses, 21, 22 (1941).
- 45 Kelkar and Limaye, C. A., 31, 2214 (1937).

THE REVERSE FRIES REACTION

Rosenmund and Schnurr found that p-hydroxyketones having an alkyl group ortho to the acyl group are converted to m-alkylphenyl esters in excellent yields on heating with sulfuric, camphorsulfonic, or phosphoric acid.

$$\begin{array}{c} \operatorname{acid.} \\ \operatorname{OH} \\ \subset \operatorname{H}_1 \\ \end{array} \xrightarrow{\operatorname{H}_1 \otimes \operatorname{O}_1} \begin{array}{c} \operatorname{OCOCH}_1 \\ \subset \operatorname{H}_1 \\ \end{array} \\ \left[\operatorname{Quantitative\ yield} \right]$$

It has been supposed that the temperature effect in the Fries reaction may be related to this reverse reaction; that is, the p-hydroxyketone may revert to the ester, which then rearranges to the o-hydroxyketone under the influence of the aluminum chloride and the high temperature. Indeed, the p-hydroxyketone shown above is converted to the isomeric o-hydroxyketone on heating with aluminum chloride. However, the ester has not been shown to be an intermediate.

SELECTION OF EXPERIMENTAL CONDITIONS

The phenyl esters are conveniently prepared by heating the phenol with the acid chloride, or, if the acid chloride is aromatic, by a Schotten-Baumann acylation. If the starting materials are pure, the crude dry Baumann acylation in the starting materials are pure, the crude dry baumann acylation.

The temperature at which the Pries reaction is best carried out depends upon whether an o- or p-hydroxyketone is being prepared, and upon the upon whether an o- or p-hydroxyketone is being prepared, and upon the reactivity of the acyl group. These factors have been discussed in several than 1. If mild experimental conditions are indicated, a solvent, usually nitrobenzene, is employed. Reaction under more severe conditions a nitrobenzene, is employed. Reaction under more severe conditions recensuly carried out without a solvent. Tetrachlorosthane and chlorostenesary useful solvents when the reaction is to be run at temperatures benzene are useful solvents when the reaction is to be run at temperatures.

In general, for the preparation of a p-hydroxylectone one mole of an ester is dissolved in about five times its weight of dry nitrobenaece, and ester is dissolved in about five times its weight of dry nitrobenaece, and from 1.2 to 1.3 moles of aluminum chloride is added in small portions. The rate of addition of the aluminum chloride is regulated by the heat. The rate of addition of the aluminum chloride is regulated by the heat evolved in the reaction. The mutture is allowed to stand for twenty-four evolved in the reaction. The mutture is allowed to 60° for an bour. It is then hours at room temperature or is heated to 60° for an bour. It is then poured onto ice and dilute hydrochloric acid.

For the preparation of an o-hydroxyketone, one mole of an ester is mixed intimately with 1.2-1.3 moles of aluminum chloride in a flask con-

nected with an air or water condenser. It is advisable to use a large flask as the mixture often foams during the reaction. The flask is placed in an oil bath, heated slowly to 120°, and kept at that temperature for fifteen minutes. The heating should be done cautiously as the heat of reaction is often large. The upper temperature may be higher than 120°, but it is desirable to keep the temperature as low as possible. After cooling, ice and dilute hydrochloric acid are added.

Boron fluoride has been used to bring about the Fries reaction, but no details of its use are available.⁴⁷

Several procedures are available for working up the reaction mixtures. Nitrobenzene or tetrachloroethane, when present, can be removed by distilling with steam. Alternatively, the reaction mixture can be extracted with ether and the product isolated by extraction of the ether solution with aqueous sodium hydroxide.

Mixtures of o- and p-hydroxyketones often can be separated by virtue of the fact that the latter are not volatile with steam. If the o-hydroxyketone is of such large molecular weight that it is not volatile with steam, a separation may be effected by distillation at ordinary or reduced pressure. Thus, o-heptanoylphenol boils at 135–140° (3 mm.) while the para isomer boils at 200–207° (4 mm.).⁴³ If the o- and p-hydroxyketones are both solids, a separation often can be effected by taking advantage of the fact that the ortho isomer will be the more soluble in ligroin. Again, it is frequently possible to separate a pair of isomeric o- and p-hydroxyketones by extracting with dilute sodium hydroxide an ether solution containing both isomers. The p-hydroxyketone is extracted more readily.

EXPERIMENTAL PROCEDURES

The Low-Temperature Reaction in Nitrobenzene

Preparation of 2-Methyl-4-hydroxyacetophenone.² To a solution of 10 g. of o-cresyl acetate in 50 g. of nitrobenzene is added in small portions 10 g. of aluminum chloride. The reaction mixture is left to stand for twenty-four hours at room temperature and then is poured onto ice and dilute hydrochloric acid. The nitrobenzene is removed by steam distillation, and the residual crude 2-methyl-4-hydroxyacetophenone is purified by vacuum distillation. The yield is 8.0-8.5 g. (80 to 85%) of pure ketone, m.p. 128°.

Meerwein, Ber., 66, 411 (1933); Auwers, Pôtz, and Noll, Ann., 535, 228 (1938).

¹⁵ Read and Wood, Org. Syntheres, 20, 58 (1940).

The Preparation of a p-Hydroxyketone in the Ahsence of a Solvent

Preparation of 3-Methyl-4-hydroxybeazophenone.* Fifty grams of o-cresyl benzoate is heated to 130° and stirred while 40 g. of aluminum chloride is added. The temperature is raised to 160° and kept there for forty-five minutes. After cooling, the reaction mixture is decomposed with dilute hydrochlorio acid, and the crude product is filtered and dried. On distillation, the material boils at 210–200° (12–15 mm.) and furnishes 455 g. (90%) of pure ketone, mp. 173–174°

The Preparation of an o-Hydroxyketone

Preparation of 2-Hydroxy-5-methylbenzophenone. In a 1-1., threenecked, round-bottomed flask fitted with a thermometer and an air condenser are placed 75 g. (0.35 mole) of p-cresyl benzoato and 60 g. (0.44 mole) of aluminum chloride. The reactants are mixed by shaking, and the flask is then placed in an oil bath at 90°. After the reaction mixture has melted, heat is applied to the bath, rapidly until the temperature of the mixture reaches 120°, then slowly until it reaches 140°. The reaction mixture is kept at this temperature for ten minutes, the thermometer is removed from the flask, and the flask is removed from the bath. When the reaction mixture is cold, it is added to a stirred mixture of 250 g of ice and 150 cc. of concentrated hydrochloric acid. After the ice has melted, the solid product is filtered and dried. The yield is 70-73 g, of a yellow solid which is pure enough for most purposes but which contains a small amount of impurity that lowers the melting point considerably. The ketone may be purified by distillation with superheated steam followed by crystallization from ethanol. ft then melts at 83-81°, and the yield is 60 g. (80%).

Formation and Separation of a Mixture of o- and p-Hydroxyketones

Preparation of o- and p-Propiophenol.* In a 2-1., three-necked, round-bottomed flask fitted with a reflux condenser, a sturdy mechanical stirrer, and a 100-cc. dropping funnel are placed 374 g. (2.8 moles) of aluminum chloride and 400 cc. of carbon dissuffice. Stirring is begun, and 375 g. of phenyl propionate is added at such a rate that the solvent boils vigorously. When the addition is complete, the reaction mixture is vigorously. When the addition is complete, the reaction mixture is vigorously. The such a such as the such as the condenser boiled on the steam hath for about two hours; then the reflux condenser is turned downward and the solvent is removed by distillation. The

Cox, J. Am. Chem. Soc., 49, 1029 (1927).
 M:ller and Hartung. Org. Syntheses, 13, 90 (1933).

flask is next heated for three hours in an oil bath maintained at 140-150°, stirring being continued as long as possible.

The reaction mixture is allowed to cool and is decomposed by the cautious addition of a mixture of 300 cc. of water and 300 cc. of concentrated hydrochloric acid, followed by 500 cc. of water. On standing overnight, most of the p-propiophenol in the upper oily layer solidifies and is removed by filtration. It is crystallized from 400 cc. of methanol and furnishes 129–148 g. (34–39%) of light yellow material melting at 145–147°. A second crystallization raises the melting point to 147–148°.

The oily filtrate and the concentrated mother liquors from the above recrystallization are dissolved in 500 cc. of 10% aqueous sodium hydroxide and extracted with two 100-cc. portions of ether to remove non-phenolic products. The alkaline solution is acidified, and the oily layer is separated, dried over anhydrous magnesium sulfate, and distilled. The distillation furnishes 120–132 g. (32–35%) of o-propiophenol boiling at 110–115° (6 mm.) and 40 g. of p-propiophenol boiling at 135–150° (11 mm.). The total yield of crude p-propiophenol is 169–188 g. (45–50%).

TABULAR SURVEY OF THE FRIES REACTION

The Tables include only reactions which yield phenolic ketones; reactions which are accompanied by or followed by cyclization, leading to hydrindones, coumarones, or other polycyclic substances, are not tabulated. A discussion of such reactions, together with an extensive table of Fries reactions, has appeared recently.⁵⁰c

The use of one mole of aluminum chloride per mole of ester is to be understood unless a different ratio of aluminum chloride to ester or a different reagent is specified. The position of the acyl group in the product is always given with reference to the hydroxyl group as 1; if more than one hydroxyl group is present, the numbering is such as to give the lowest numbers to the carbon atoms carrying the hydroxyl groups. Where a product is listed but no yield is given, the product was reported in the literature with no information about the yield.

122 Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," American Chemical Society Monograph Series, No. 87, pp. 696-709, Reinhold Publishing Corporation, New York, 1941.

A. ESTERS OF PHENOL

Ester			Products		Refer-
R of Acyl Group	Solvent	Experimental Conditions	%2-Acyl	% 4-Acyl	ence '
CH ₁ CH ₂ CH ₃ CH ₃ CH ₁ CHIn CHIn CHIn CHIn CHIn CHIn CHIn CHIn	C.H.B.NO. CS. CHCI.CHCI.CHCI.CHCI.CHCI.CHCI.CHCI.CH	24 hr. at 20-25° 165° 25hr. at bp , 3hr at 140- 150° 1-2 hr. at 160-150° 1-2 hr. at 160-150° 1-2 hr. at 160-150° 2 AlClij 6 hr. at 70° 2 AlClij 6 hr. at 70° 2 AlClij 6 hr. at 70° 15 min. at 140° 10 hr. at 70°	70 max. 30 60 50 33 5 30 20 1 58 28 Second- ary 34 5 14 9 18 3 Second- ary	43 19 7 21 2	3 3 51 11 10 10 10 10 3 11 3 10 14

^{*}Gomparable results are reported * with the phenyl esters of other primary, straight-chain, abphasic

brids up to and including caprylic acid.

Pemethylation at the other hakage takes place

B. Esters of Monosubstituted Phenols

Ester			Products		
Substituent	R of Acyl Group	Experimental Conditions	% 6-Acyl	%4-Acyl	Reference
2-CH ₃	CH ₃	C ₆ H ₅ NO ₂ ; 24 hr. at 20°	_	85 °	3
2-CH ₃	CH ₃	?	55 max.	i —	3
2-CH ₃	CH ₂ Cl	140°	20	No yield	52
2-CH ₃	C ₂ H ₅	3 hr. at 120°	40	No yield	53
2-CH ₃	C ₃ H ₇	Overnight at room temper- ature, heat to 100-110°	No yield		17
2-CH ₃	C ₃ H ₇	½ hr. at 160-180°	60	30	11
2-CH ₃	C_3H_7	48 hr. at room temp.		30	11
2-CH ₃	C ₄ H ₉	½ hr. at 160~180°	46	30	11
2-CH ₃	C5H11	½ hr. at 160–180°	60	25	11
2-CH ₃	C ₆ H ₅	15 min. at 140°	-	Quanti- tative	3
2-CH ₃	C ₆ H ₅	Add reagent at 130°; 45 min. at 160°	-	91	49
2-C2H5	CH ₃	100-120°	No yield		16
2-C ₆ H ₅ CH ₂	CH₃	C ₆ H ₅ NO ₂ ; overnight at room temp., 3-4 hr. at 50-60°	- -	70 ⁵	7
$2C_6H_5CH_2$	CH₃	170°		No yield	7
3-CH ₃	CH ₃	C ₆ H ₅ NO ₂ ; 24 hr. at 20°		82 €	3
3-CH ₃	CH ₃	165°	95		3
3-CH ₃	CH ₂ Cl		50	_	54
3-CH ₃	C_2H_5	C6H5NO2; 10 days at 2°	65	10	4
3-CH ₃	C_2H_5	120-140°	93	_	4
3-CH ₃	C ₃ H ₇	C6H5NO2; 10 days at 2°	72	3	4
3-CH ₃	C_3H_7	120-140°	75	_	4
3-CH ₃	C ₃ H ₇	C ₆ H ₅ NO ₂ ; 24 hr. at 20°	88	_	11
3-CH ₃	C ₄ H ₉	C ₆ H ₅ NO ₂ ; 24 hr. at 20°	85	_ 1	11
3-CH ₃	C ₄ H ₉	120-140°	80	_	4
3-CH ₃	C ₅ H ₁₁	C ₆ H ₅ NO ₂ ; 24 hr. at 20°	93	_	11
3-CH ₃	C_5H_{11}	120-140°	91	_ [4
3-CH ₃	C_6H_5	C ₆ H ₅ NO ₂ ; 5 hr. at 60°	_	60	3
3-CH ₃	C ₆ H ₅	15 min. at 175°	95	_	3
3–CH₃	C ₅ H ₅	CS ₂ ; 3 hr. at room temp., heat to 90°	50	32	49
3-CH ₃	C_6H_{13}	C ₆ H ₅ NO ₂ ; 24 hr. at 20°	84	_	11
3-CH ₃	C6H13	120–140°	67	_	4
3-CH ₃	C ₈ H ₁₇	120–140°	75	-	4

^{*} References 51-64 appear on p. 369.

B. Esters of Monosubstituted Phenois-Continued

Ester			Prod	ucts	Refet
Substituent	R of Acyl	Experimental Conditions	%2-Acyl	% 4-Acyl	ence
	Group		90 d		3
-CH ₂	CH ₃	10 min. at 120°	90		54 55
-CH ₃		4 hr. st 140° Cold 45 min., warm on	80	-	20
-CH ₃	C ₂ H ₅	steam bath			11
	CaH ₀	2 br. at 160°	65 88	-	3, 1
-CH ₂ -CH ₃	C ₄ H ₁₁	10 min, at 120°	Quanti-		3
-CH	CdI	10 min. at 140°	tative"	1	l
i-CH ₂	Cells	15 min. at 140°; heat to		-	49
		200*	85	-	3
-CH ₃	C4II13	10 min. at 120° 20 min. at 100°	Quanti	-	1 .
i-CH _i	C7H16		Quanti		53
⊢CI	CH ₁	I hr. at 120°	tative	1 -	56
ı-CI	CTT₂CT	5 hr. at 140-150*	No yiel	-	16
i-Ci i-Cilli	CH	61 br. at 100-110°	No yie	d -	17
4-C ₄ H ₂	CH ₂	, and the state of the	854	1	
4-C ₆ H ₆ CH ₂	CIIs	C4H4CI; 30-45 min. at b p C4H4CI; 30-45 min. at b.p		-	
4-CallaCHaCHa 4-CallaCHaCHaCHa	CII:	CellaCl; at b.p.	No yie	d	1

^{*} Comparable results are reported 8 with the e-creay enters of other pumary, straight-chain, alighetic

nute up to end including copyline and

Comparable results are reported? with the propionate, butyrate, and mobutyrate of a-bearylpheol

Comparable results are reported? with the propionate, butyrate, and mobutyrate of a-bearing acids up to end including copcylio and Comparable reside are reported a wish the propionate, butyrate, and monutrates of the Comparable reside are reported a wish retors of as exceed and primery, straight-obsern, alphane. edds up to end including caprylar edd. These results here not been confirmed, it is compare the date in

^{*}Comparable results are reported? with the propionate, butyrate, and isovalerate of p-creed the table above for three rates of mercent

^{*} Comparable results are reported a with the e-chlorobenesate, the obcombineste, and the pbromobensosta of percent

components of percessi. Comparable results are reposted t with other eliphatic acid exters of p-oblorophesos and of p bromophenol

Compersion results are reported I with the preplomate, butyrete, and isovalerate of p-benzylphenol.

Comperable results are reported? with the prophorate, butyrate, and novacrase or prophorate Comperable results are reported? with the prophorate, butyrate, and hovalerate of p-(p-phonytethyl)-phenol.

C. Esters of Disubstituted Phenols

Ester	-		Produ	icts	
Substituent	R of Acyl Group	Experimental Conditions	% 6-Acyl	% 4-Acyl	Refer- ence *
2,3-Dimethyl	CH₃	18 hr. at room temper- ature, heat to 120°	60		16
2,3-Dimethyl	CH₃	Heat on steam bath	69		57
2,4-Dimethyl	CH ₃	130-140°	No yield		15
2,4-Dimethyl	C6H13	130-140°	74	-	17
2-Methyl-4-ethyl	CH₃	6 hr. at 130-140°	77		16
2-Methyl-4-ethyl	C_2H_5	3 hr. at 130-140°	70		17
2-Ethyl-1-methyl	CH ₃	130-140°	No yield		15
2,4-Diethyl	CH₃	$5\frac{1}{2}$ hr. at 130–140°	67		16
2-Methyl-4-butyl	CH ₃	130-140°	63		17
2-Ethyl-4-propyl	CH₂	?	No yield		17
2-Chloro-4-methyl	CH₂	10 min. at 120°	Quanti- tative ^a	-	3
2-Chloro-4-methyl	C _c H ₅	10 min. at 140°	92		3
2-Ethyl-4-chloro	CH ₃	2 hr. at 120°	No yield		53
2,5-Dimethyl	CH₂	18 hr. at room temper- ature, heat to 120°	2,4- Dimethyl- 6-acetyl, 17	70	15
2-Ethyl-5-methyl	CH ₃	130–140°	2-Ethyl- 4-methyl- 6-acetyl,	-	15
2-Methyl-5- isopropyl	CH ₂	C ₆ H ₈ NO ₂ ; 24 hr. at 25°	_	90°	3
2-Methyl-5- isopropyl	CeH5	C ₂ H ₅ NO ₂ ; 5 hr. at 60°	-	69	3
2-Propyl-5-methyl	CH ₂	C ₅ H ₅ NO ₂ ; 18 hr. at 20°	_	82	3
2-Isopropyl-5- methyl	CH2	CeH5NO2; 24 hr. at 20°		87 °	3
2-Isopropyl-5- methyl	C ₆ H ₅	C ₅ H ₅ NO ₂ ; 5 hr. at 60°		70	3
2-Isopropyl-5- methyl	C _€ H ₅ CH=CH	C ₂ H ₅ NO ₂ ; 48 hr. below 20°	-	80	3
2,6-Dimethyl	CH₃	Overnight at room temp., 6 hr. at 120°	-	81	16

^{*} References 51-64 appear on p. 369.

 $^{^{\}circ}$ Comparable results are reported $^{\circ}$ with the propionate and butyrate of 2-chloro-i-methylphenol.

Comparable results are reported? with the propionate, butyrate, and isoralerate of carracrol.

Comparable results are reported? with the propionate, butyrate, isoralerate, phenylacetate,

capsylste, and hydrocinnamate of thymol.

C. Esters of Disubstituted Phenois-Continued

Ester			Produc	ts	
Substituent	R of Acyl	Experimental Conditions	% 8-Acyl	% 4-Acyl	Refer- ence
	C ₁ H ₅	Overnight at room		59	17
,6-Dimethyl	C ₃ H ₇	temp, heat at 100- 110°		67	17
,	CaHa	temp., heat at 100- 110°	-	47	17
9,6-Dimethyl		temp., heat at 100- 110°		65	17
2,6-Dimethyl	C ₆ H ₁₃	temp., heat at 100- 110° Overnight at room	_	75	17
2,6-Dimethyl	CuHs	temp., beat at 100-	2-Methyl	. 50	16
2-Methyl-6-ethyl	CIL	5 hr. at 130-140°	4-ethyl- 6-acetyl		17
2-Methyl-6-ethyl	C ₂ H ₄	Overnight at room temp., heat to 100- 110*	ļ		
2,6-Diethyl	CH,	100-120*	Unidenti fied o-hydrov yketone		16
2-Methyl-6-propy	CH;	*	-	No yield	17
	CH	4 hr. at 130°	No yield		16
3.4-Dimethyl 3-Methyl-4-ethyl	CHs	4½ hr. above 100° 10 min. at 120°	Quanti-	-	3
3-Methyl-4-ethyl	1	10 min. at 120°	No yield		3
3-Methyl-1-chlor 3-Methyl-1-chlor	Clis C ₆ H ₈	10 min. at 140°	Quanti-		3
3,5-Dimethyl 3,5-Dimethyl	Cll ₂	10 hr. on steam bath 2 hr. on steam bath	No yield	diary	rl I
	CHs	10 hr at 100-120°	No yield		16

ethylphetol

* Under the same conditions the propions is and butyrate of 3-methyl-4-chlorophetol are reported to
(much the 6-ex) derivatives in yields of more than 80%.

D. ACETATES OF TRISCBSTITUTED PHENOLS

Substituents	Experimental Conditions	Products	Reference *
2,3,4-Trimethyl	130-140°	6-Acetyl	15
2,3,5-Trimethyl	2½ hr. at 130–140°	2,3,4-Trimethyl-6-acetyl, 86%	15
2,4,5-Trimethyl	4 hr. at 130–140°	2,3,4-Trimethyl-6-acetyl, principal 2,4,5-Trimethyl-6-acetyl,	15
	The second secon	considerable 3,4-Dimethyl-6-acetyl,small 2,3,5,6-Tetramethylphenol, very small	,
2,4-Dimethyl-5-ethyl	6 nr. at 130–140°	2,4-Dimethyl-3-ethyl-6- acetyl, principal 2,4-Dimethyl-5-ethyl-6- acetyl, secondary Total yield, 75%	16
2-Ethyl-4,5-dimethyl	6½ hr. at 130–140°	2-Ethyl-4,5-dimethyl-6-	16
		acetyl 2-Ethyl-3,4-dimethyl-6- acetyl	
2,4-Diethyl-5-methyl	5 hr. at 139–140°	2,4-Diethyl-5-methyl-6- acetyl 2,3-Diethyl-4-methyl-6- acetyl Total yield, 65%	16
3.4.5-Trimethyl	$\frac{1}{2}$ hr. at 139°	2-Acetyl	15
2,4,6-Trimethyl	11 hr. at 130–140°	•	15, 17
2,4-Dimethyl-6-ethyl	7 hr. at 130–140°	2,4-Dimethyl-3-ethyl-6- acetyl, principal 2-Ethyl-3.4-dimethyl-6- acetyl, secondary Total yield, 70%	16, 17
2,6-Dimethyl-4-ethyl	5 hr. at 130–140°	2,6-Dimethyl-4-acetyl 2,4-Dimethyl-6-acetyl 2,4-Dimethyl-3-ethyl-6-acetyl Total yield, 50%	17 Cf. 16
2-Methyl-4,6-diethyl	7 hr. at 139–140°	2-Methyl-3,4-diethyl-6- acetyl, 70%	16, 17
2,6-Diethyl-4-methyl	5 hr. at 139–140°	2,3-Diethyl-4-methyl-6- acetyl, 60%	16

^{*} References 51-64 appear on p. 359.

D. ACETATES OF TRISURSTITUTED PRENOLS-Continued

Substituents	Experimental Conditions	Products	Reference *
2,6-Dimethyl-4-propyl	130-140°	2,6-Dimethyl-4-acetyl, 46% Unidentified o-hydroxyke- tone, 1%	17
2,6-Dimethyl-4-butyl	3 hr. at 130–140°	2,6-Dimethyl-4-acetyl, 40% Unidentified o-hydroxyke- tone, 10%	17
2-Methyl-4-ethyl-6-allyl	4 hr. at 130–140°	2-Methyl-4-ethyl-6-acetyl, 50%	17
2-Methyl-4-ethyl-6- propyl	130-140°	2-Methyl-6-propyl-4-acetyl, 25% Unidentified o-hydroxyks- tone, 25%	17
2-Methyl-4-propyl-6-cthyl	3 hr. at 130–140°	Unidentified e-hydrovyke- tone, 30%	17
2,4,6-Triethyl	6 hr. at 130-140°	2,3,4-Triethyl-6-acetyl, 65%	16 17
2-Methyl-4-butyl-6-ethyl	4 hr. at 130-140°	2-Methyl-4-butyl-6-acetyl,	17
2.6-Dimethyl-4-benzyl	3 hr. at 130-140°	2.6-Dimethyl-Lacetyl, 65%	17
2,4-Dimethyl-6-heptyl	3 hr. at 130-140°	Unidentified o-hydroxyke- tone, <50%	17
2,6-Dimethyl-4-heptyl	4 hr. at 130-140°	2,6-Dimethyl-4-acetyl, 18% Unidentified o-hydroxyke- tone, 3.5%	17
2-Methyl-4-ethyl-6-benzyl	4 hr. at 130-140°	2-Methyl-1-ethyl-6-acetyl, 63%	17
2-Methyl-4-heptyl-6-ethyl	130-140"	Unidentified o-hydroxyke- tone, 33%	17
2,6-Dimethyl-4-dodecyl	8 hr. at 130-140°	2,6-Dunethyl-4-acetyl, 20%	17
2-Methyl-4-dodecyl-6- ethyl	3 br at 130-140°	2-Methyl-6-ethyl-1-acetyl, 5%	17

^{*} References 51-64 appear on p. 369

E. ESTERS OF POLYHYDROXYBENZENES

Ester	Solvent	Experimental Conditions	Products	Reference
Catechol diacetate Catechol dipropionate		2 hr. at 75° 45 hr. at room temp., warm on steam bath	4-Acyl, 89% 4-Acyl, 39%	18 18
Catechol dibutyrate	C.H.NO.	$\frac{1}{2}$ hr. at 100°	4-Acyl, 35%	18
Catechol dibutyrate		Add 1 mole catechol; 2 hr. at 80°		18
Catechol divalerate	CS ₂	Add 1 mole catechol;	4-Acyl, 50%	19
Catechol diiso- valerate	CS ₂	Same as divalerate	4-Acyl, 69%; 3-acyl	19
Catechol diiso- valerate	C:H:NO	Add 1 mole catechol; 1 hr. at 80°	4-Ac7l, 40%	18
Catechol dicaproate	CS₂	Same as divalerate	4-Acyl, 72%	19
Catechol diiso- caproate	CS2	Same as divalerate	4-Acyl, 60%; 3-acyl	19
Catechol dibenzoate	C:H:NO2	4 hr. at 100°	+Acyl, Quantitative	18
Catechol distearate	_	1 hr. at 110°	No pure product	18
Gusiscol scetate		ZnCle; heat to b.p.	4-Acyl, 26%; 5-acyl, 5.6%; 6-acyl, 1%	27
Guaizcol acetate	C ₂ H ₂ NO ₂	3 days at room temp.	4-Acyl, 30%	18
Gusiacol propionate	CtHiXO	2AlCh; ½-1 hr. at 80°, overnight cold		11
Guaiacol propionate		2AlCh; 2 hr. at 140°	4-Acyleatechol, 51%	19
Gusiacol butyrate	CS ₂	Same as propionate in CS2	4-Acylestechol, 23-	19
Guaiscol caproste	CS ₂	Same as propionate in CS ₂	4-Acylestechol, 30-	19
Guaiacol heptanoate	CS ₂	Same as propionate in CS ₂	4-Acylestechol, 8-	19
Resorcinol diacetate	-	2AlCl ₂ ; 4 hr. at 130°	2,6-Discyl 5	22
Resorcinol diacetate	_	ZnCl2; 139°	2,6-Discyl, 49-50%	20
Resorcinol mono- methyl ether acetate	7	24 hr. at room temp.	4-Acyl, 11%; 6- acyl, 12%	26
4-Ethylresorcinol	C.H.NO.	2AlCl. Add 1 mole	6-Acyl, Quantita-	22
diacetate	Control Control	of 4-ethyl resor- cinol; 18 hr. at room temperature.	tive 2	
	9	3-4 hr. at 60°		
	*		·	

^{*} References 51-54 appear on p. 309.

Comparable results are reported " with the busyrate, valence, and heptatosite.

Comparable results are reported = with the dipropionate, dibutyrate, and divalente.

Comparable results are reported = with the dipropionate, dibusyrate, dimproate, and dilayrate.

Without the added mule of 4-ethylrescrainol, the yield is 47%. Comparable results are reported = with the dipropionate, dilutyrate, disconferate, diagrante, and dilensoate.

E. ESTERS OF POLTHYDROXYBENZENES-Continued

Ester	Solvent	Experimental Conditions	Products	Reference
4-Ethylresorcinol	-	2AlCl ₃ ; 3-4 hr. at 60		22
4-Ethylresoreinol dipropionate	-	70° or 5 hr. at 110 2AlCl ₂ ; 3–4 hr. at 60 70° or 5 hr. at 110	- 2,6-Diacyl, 50%	22
4-Propylresorcinal diacetate	C ₈ H ₈ NO ₂		- 6-Acyl*	22
4-Propylresorcinol diacetate		2AlCl ₃ ; 4hr at 60-70		22
5-Methylresorcinol, 1-acetate 3-mono- methyl ether	C'H'NO	24 hr. at room test- perature	6-Acyl, 50%	26
4-Benzylresorcinol diacetate	C*H*NO	Add one mole of 4- benzylresorcinol, 3-4 hr. et 50°	6-Acyl, 85%	7
Hydroquinone di- acetate	C4II ⁴ NO ³	2 hr. at 75°	2-Acyl, 23%	18
Hydroquinone di- propionate	C.H.NO	2 hr. et 75°	2-Acyl, 21%	18
Pyrogallol triacetate		ZnCl2; 2 hr. et 145°	5,6-Diacy1, 26%	28
Pyrogallol monoace- tate dimethylether (1.2.3)		24 hr at room tem- perature	6-Acyl, 61%	26
Pyrogallol monoace- tate dimethylether (1.2.6)		24 hr at room tem- perature	4-Acyl, 7 5%	32
Pyrogallol monoace- tate dimethylether (1,2,6)	- [ZnCl ₂ ; 3 hr. et 120*	3-Acetyl-6-methoxy- 1,2-dihydroxyben- zene, 8%	31
Pyrogaliol monuace- tate dimethylether (1,2,6)	CHCOCI	ZnCl ₂ ; 4 weeks at room temperature	3-Acetyl-6-methoxy- 1,2-dihydrovyben- zene, 10%	31
Pyrogallol mono- ehloroacetate di- methylether (1,2,6)	-	8 hr. at 100°	3-Chlorowetyl- pyrogallol	31

• References 51-64 appear on p 369

^{*}Comparable results are reported is with the diproposante, dibutyrate, dirabrate, dicaproate, and

dibensorie.

Comparable results are reported? with the diproponate, dibutyrate, and discovalerate of 4-bensyl-resoccased and with the same setters of 4-6-phenylethyl)-resoccased.

E. ESTERS OF POLYHYDROXYBENZENES—Continued

Ester	Solvent	Experimental Conditions	Products	Reference *
Trihydroxybenzene, 1,4-diacetate-2- methyl ether	$\mathrm{C_6H_5NO_2}$	24 hr. at room tem- perature	5-Acyl, 38%	26
Phloroglucinol tri- acetate		ZnCl ₂ ; 3 hr. at 130°	2,4,6-Triacetyl- phloroglucinol, 60%	20, 29
Phloroglucinol tri- acetate	$\mathrm{C_6H_5NO_2}$	24 hr. at room tem- perature	2,4,6-Triacetyl- phloroglucinol, 28%	30
Phloroglucinol tri- benzoate	_	30 min. at 130-140°	2,4,6-Tribenzoyl- phloroglucinol, 30%	18

F. Esters of Naphthols, Hydroxybiphenyls, and Hydroxyphenanthrenes

Ester	Experimental Conditions	Products	Refer- ence *
α-Naphthyl acetate	C ₆ H ₅ NO ₂ ; 18 hr. at 0°	2-Acyl, 16%; 4-acyl, 42%	12
α-Naphthyl acetate	C ₆ H ₅ NO ₂ ; 18 hr. at 25°	4-Acyl, 28%	12
α-Naphthyl acetate	2 hr. at 100°, 1 hr. at 120°		13
α-Naphthyl acetate	4 hr. at 125°	2-Acyl, 50%	34
α-Naphthyl acetate	½ hr. at 150°	2-Acyl, 25%; 4-acyl, 10%	60
α-Naphthyl propionate	2 hr. at 100°; 1 hr. 120°	2-Acyl, 54%; 4-acyl, 6%; 2,4-diacyl, 2%	13
α-Naphthyl butyrate	C ₆ H ₅ NO ₂ ; 18 hr. at 0°	2-Acyl, 22%; 4-acyl, 35%	12
α-Naphthyl butyrate	2 hr. at 100°; 1 hr. at 120°	2-Acyl, 55%; 4-acyl, 3%; 2,4-diacyl, 2%	13
α-Naphthyl valerate	2 hr. at 100°; 1 hr. at 120°	2-Acyl, 40%; 4-acyl, 2%	13
α-Naphthyl phenylace- tate	C ₆ H ₅ NO ₂ ; 24 hr. at 0-10°		12

^{*} References 51-64 appear on p. 369.

F. Esters of Naphthols, Hydroxybiphentls, and Hydroxyphenanthrenes—Continued

Leter	Experimental Conditions	Products	Reference *
α-Naphthyl benzoate	Room temperature in CaHaNO2 or b p. in CS	No reaction	12
β-Naphthyl acetate	CS ₂ ; 1 hr. at b.p., 4 hr. at 120°	1-Acyl, 40%	31
β-Naphthyl acetate	30 min, at 120°	I-Acyl, 33%	60
β-Naphthyl acetate	ZnCl ₂ ; 150–160°	6-Acyl, 5%	33
8-Naphthyl chloro- acetate	CS ₂ ; 1 hr. at h p., 4 hr. at 120°	Naphtho[2,1-5] furan, 1,2-dshydro-1-one, 20%	61
2-Hydroxybiphenyl acetate	3 hr. at 130°	5-Acyl, 60%; 3-acyl	37
2-Hydrovyhiphenyl propionate	30~45 min. at 160°	5-Acyl; 3-acyl, 8%	38
2-Hydroxybiphenyl butyrate	30-45 min. at 160°	5-Aeyl, 40%, 3-acyl, 15%	38
2-Hydroxybiphenyl valerate	30-45 min. at 160°	5-Acyl, 40%; 3-scyl, 20%	35
3-Hydroxybiphenyl pro- pionate	30-45 min at 160°	4-Acyl, 71%	38
4-Hydroxybiphenyl	CFICl ₂ CHCl ₂ ; 2 hr at 140°	3-Acyl	40
4-Hydroxybiphenyl acetate	CS ₂ ; 30 min at 140°	3-Acyl; 4'-acyl, 4%	9
4-Hydroxybiphenyl henzoate	CHCl ₂ CHCl ₂ ; 1 hr. at	4'-Acyl	6
4-Hydroxybiphenyl henzoate	CHCl ₂ CHCl ₂ ; 1 hr. at	3-Acyl	39
4-Hydroxybiphenyl benzoate	CS2, ½ hr. at 160°	4'-Acyl, 22%	9
2-Hydroxyphenauthrene acetate	7	Mixture contains over 10% t-acyl	36
3-Hydroxyphenanthrene acetate	AICIs or AlBra	No crystalline product	36
9-Hydroxyphenanthrene acetate	AlBr ₃ ; C ₆ H ₅ NO ₂ ; 2 ¹ / ₂ hr. at room temperature	10-Acyl	36
2-Hydroxy-9,10-dihydro- phenanthrene acetate		3-Acyl, 24%; 7-acyl, 23%	62

^{*} References 51-64 appear on p 369.

THE FRIES REACTION

G. ESTERS OF HYDROXYCOUMARINS

Ester	Experimental Conditions	Products	Reference *
4-Methyl-5-hydroxy- coumarin acetate	?	6-Acyl	44
4-Methyl-7-hydroxy- coumarin acetate	1 hr. at 120–140°	8-Acyl, 15-20%	63
4-Methyl-7-hydroxy- coumarin acetate	1 hr. at 140–150°	6-Acyl, 4%; 8-acyl	41
4-Methyl-7-hydroxy- coumarin acetate	Rapidly to 125°; then heat during 2 hr. to 170°	8-Acyl, 75%	45
4-Methyl-7-hydroxy- coumarin propionate	I hr. at 165–170°	8-Acyl, 28%; 6-acyl	64
4-Methyl-7-hydroxy- coumarin benzoate	1 hr. at 160-170°	8-Acyl, 63%	42
4-Methyl-7-hydroxy- coumarin p-toluate	?	8-Acyl	64
4-Phenyl-7-hydroxy coumarin acetate	I hr. at 165–170°	8-Acyl, 50%	43
4-Phenyl-7-hydroxy- coumarin benzoate	1 hr. at 165–170°	8-Acyl	43
4-p-Bromophenyl-7- hydroxycoumarin acetate	?	8-Acyl	43
4-p-Tolyl-7-hydroxy- coumarin acetate	I hr. at 165°	8-Acyl, 7%	64

^{*} References 51-64 appear on p. 369.

TABULAR SURVEY OF THE FRIES REACTION

H. Some Mescellanenes Espers

Ester	Experimental Conditions	Products	Reference
Acetylsalicyclic acid	CellsNO2; 4 hr at 60°	4-Aeyl, 60%	3 8
Caproyladicylic acid, methyl ester 2-Acetyl-1-methylphenyl	CS ₂ ; 2 hr. at b.p., heat to 110° 10 min. at 100–120°	4-Acyl, 82% * 2,6-Dincyl, 76%	3
acetate 2-Benzoyl-1-methyl-	7	No reaction	3
phenyl benzoate Phenyl-o-(anisoyl)	CHCl ₂ CHCl ₂ ; 2 hr. at	Phenolphthalein 90%	6
benzoate Diphenyl phthalate	OHCHCHCh; hr. at 150°	Phenolphthulem, 63% 1-llydroxyanthra- quinone, 33%	6

Comparable results are reported ⁸ for the proposate, butyrate, valerate, and moraprylate.

at Mosingo, Org. Syntheses, 21, 45 (1941)

¹¹ Auwers, Ber , 49, 812 (1916).

¹¹ Auwers and Wittig, Ber , 67, 1270 (1924). 14 Fries and Finek. Ber , 41, 4271 (1908).

⁴ Auwers, Ber., 47, 3319 (1914)

¹⁶ Fries, Hasselbach, and Schooder, Ann , 405, 369 (1914).

W Smith and Opie, J Org Chem . 6, 427 (1941).

M Auners, Ber., 48, 90 (1915). 39 Auwers and Borsche, Ber , 48, 1708 (1915).

⁴⁰ Imoto, J. Chem. Soc Japan, 58, 932 (1937) [C. 4., 32, 534 (1933)]. 11 Fries and Frelletedt, Ber., \$4, 717 (1921).

¹⁴ Mosettig and Stuart, J. Am. Chem. Soc., 61, 1 (1939).

¹² Limaye, Ber , 65, 375 (1932).

¹⁴ Limaye and Shenolikar, C. A., 33, 2096 (1938).

CHAPTER 12

THE JACOBSEN REACTION

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INTRODUCTION

The migration of an alkyl group or a halogen atom in a sulfonic acid derived from a polyakylbenzene, a halogenated polyakylbenzene, or a polyhalogenated benzene is known as the Aacobsen reaction. The reaction is nearly always effected by treating the hydrocarbon or halogenated hydrocarbon with concentrated sulfuric acid and allowing the resulting sulfonic acid to remain in contact with the sulfuric acid. The first observation of a rearrangement of this kind was made by Herzig ¹ (1881), who recorded the rearrangement of a polyhalogenated benzenesulfonic acid. However, the reactions have taken the name of Oscar Jacobsen? (1889), who discovered the rearrangement of polyalkylbenzenesulfonic acids.

The migrations of the Jacobsen reaction may be divided into two general types: (a) intramolecular, in which the migrating group moves from one position to another in the same molecule; and (b) intermolecular, in which there is a transfer of one or more groups from one molecule to another. In most cases, migrations of both types occur simultaneously. An important characteristic of the reaction is the migration of the alkyl groups to vicinal positions. The rearrangement of durenesulfonds and is a twical example.

Herzig, Ber., 14, 1205 (1881).
 Jacobsen, Ber., 19, 1209 (1886).

It is known with certainty that the rearrangements of the Jacobsen reaction involve the sulfonic acids, not the hydrocarbons.2 This is shown by the fact that durenesulfonic acid rearranges in contact with phosphorus pentoxide, a reagent which has no effect on durene itself. Also, the sulfonic acid from pentamethylbenzene rearranges when left in a desiccator over concentrated sulfuric acid, whereas the hydrocarbon is unchanged under the same conditions. As yet no completely satisfactory explanation has been advanced regarding the function of the sulfonic acid group in promoting the rearrangement.4 Nor is it possible to account for the side reactions which occur during the course of the Jacobsen reaction. The by-products are sulfur dioxide and polymeric materials ranging from tars to insoluble, infusible solids. It is known that part of the sulfur dioxide is in some way liberated from the sulfonic acid during rearrangement, while the remainder results from the oxidizing action of sulfuric acid on the organic substances present in the reaction mixture.

THE SCOPE OF THE REACTION

The Jacobsen reaction has been limited, with few exceptions, to the polyalkylbenzenes, halogenated polyalkylbenzenes, and halogen derivatives of benzene. The substituents which have been shown capable of migration are CH_3 and C_2H_5 (the only two alkyl groups studied), I, Br, Cl, and SO_3H . No Jacobsen rearrangement of compounds containing amino, nitro, methoxyl, or carboxyl groups is known.

The ease with which rearrangement takes place depends on the groups attached to the benzene ring. If only halogen is present, rearrangement occurs even when the benzene ring carries but one substituent. If both halogen and alkyl groups are attached to the ring, then rearrangement occurs the more readily the greater the number of alkyl groups, provided that at least one unsubstituted position is present. If only alkyl groups are present, then rearrangement occurs only with the tetra- and penta-alkyl derivatives. Thus, the sulfonic acids derived from the trialkylbenzenes, hemimellitene, pseudocumene, mesitylene, 1,2,4-triethylbenzene, and 1,3,5-triethylbenzene eare stable to sulfuric acid.

The synthetic value of the Jacobsen reaction lies in the formation of vicinal derivatives by migration of the alkyl groups of compounds containing these groups in non-vicinal positions. Thus, the tetramethyl-tetraethyl- and trimethylethyl-benzenes of non-vicinal orientation rear-

Smith and Cass, J. Am. Chem. Soc., 54, 1614 (1932).

⁴ Moyle and Smith, J. Org. Chem., 2, 112 (1937).

¹ Smith and Moyle, J. Am. Chem. Soc., 55, 1 (1995).

⁴ Smith and Guss, J. Am. Chem. Soc., 62, 2631 (1940).

range to valuable vicinal derivatives. This is in direct contrast to the orienting effects in rearrangements brought about by aluminum chloride.* In the polyalkylation of benzene by the Friedel and Crafts method, non-vicinal derivatives are formed. For instance, it is certain that the trimethylbenzene fraction produced from benzene, methyl chloride, and anhydrous aluminum chloride contains no 1,2,3-trimethylbenzene (hemimellitene), nor does the tetramethylbenzene fraction contain any I,2,3,4-tetramethylbenzene (prehnitene). The fact that alkyl groups orient themselves in the meta positions in the Friedel and Crafts synthesis may be ascribed to rearrangement of the expected products under the influence of aluminum chloride. Thus, it has been demonstrated that 1,3-dimethyl-1-4-butylbenzene is converted to the 1,3,5-isomer by aluminum chloride.

$$\bigoplus_{\substack{C \cap I_1 \\ C \cap C \cap I_2 \setminus I_3}}^{C \cap I_2} \xrightarrow{A \cap C_{I_2}} (C \cap I_2)_{A}$$

$$\stackrel{C \cap I_3}{\longrightarrow} C \cap I_3$$

In the halogenated polyalkylbenzenes migration of an alkyl group has been observed only with chlorodurene and chlorosodurene. Several examples of halogen migration are known. In certain cases migration of an alkyl group occurs after the removal of halogen by intermolecular rearrangement The only applications of synthetic value in connection with the rearrangement of halogenated polyalkylbenzenes are the preparations of 2,4-dibromo- or 2,4-dichloro-m-xylene from the 4,6-dihalo-mxylenes, and of 3-bromo- or 3-chloro-pseudocumene from the 5-halo isomers

The rearrangement of halogenated benzenes leads to mixtures from which pure products can be separated only with difficulty. Consequently, the method cannot be considered of synthetic value. The observations which have been reported do not indicate any tendency toward vicinal orientation in the polyhalogenated rearrangement products.

In the following section are given the detailed results of investigations of the Jacobsen reaction.

For a review of the subject of alkylation and rearrangement in the presence of aluminum chloride, see Nightingale, Chem. Rev. 25, 329 (1939).

Smith and Cass, J. Am Chem. Soc., 54, 1617 (1932).

Smith and Perry, J. Am Chem. Soc , \$1, 1411 (1939).

EXAMPLES OF THE JACOBSEN REACTION

Polyalkylbenzenes

Tetramethylbenzenes. The equation for the rearrangement of durenesulfonic acid ^{2, 3} is shown on p. 371. Prehnitenesulfonic acid has been obtained in 70% yield when the reaction was carried out by sulfonating durene with concentrated sulfuric acid and allowing the sulfonation mixture to stand for twenty-five days at room temperature.³ The other products were sulfur dioxide, carbon dioxide, and very small amounts of 5-pseudocumenesulfonic acid and hexamethylbenzene. About 30% of the reaction product was a brown amorphous material.

Isodurenesulfonic acid rearranges to prehnitenesulfonic acid, but the yield is somewhat less than that obtained from durene.^{3, 9} The byproducts are essentially the same as those from durene.

$$\begin{array}{c|c} CH_3 & CH_3 \\ \hline CH_3 & CH_3 \\ \hline CH_3 & CH_3 \\ \hline CH_3 & CH_3 \\ \hline \end{array}$$

Prehnitene is sulfonated by sulfuric acid, and the sulfonic acid does not rearrange.³

The 1,2,4,5- and 1,2,3,5-tetraethylbenzenes ^{6,10,11} rearrange to give products analogous to those obtained from the tetramethyl derivatives. However, the reactions with the tetraethylbenzenes are much more rapid (15 minutes at 100°), and the yield of 1,2,3,4-tetraethylbenzene is 90–92%. The rearrangements of the tetraethylbenzenes are the only recorded instances of Jacobsen reactions in which the tarry, polymeric by-product is entirely absent and practically no sulfur dioxide is evolved.

Ethyltrimethylbenzenes.^{12, 13} The sulfonic acids of 1,2,4-trimethyl-5-ethylbenzene (5-ethylpseudocumene) and 1,3,5-trimethyl-2-ethylbenzene (ethylmesitylene) rearrange to that of 1,2,4-trimethyl-3-ethylbenzene (3-ethylpseudocumene). The yields are relatively low, owing to side reactions which involve elimination of the ethyl group or one of the methyl groups. In the chart on p. 375, the sulfonic acid groups are not included in the formulas because their exact positions are unknown.

² Töhl, Ber., 21, 904 (1888).

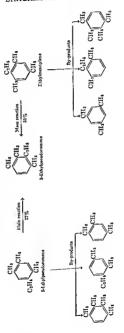
¹⁵ Jacobsen, Ber., 21, 2814, 2819 (1888).

¹¹ Galle, Ber., 16, 1774 (1883).

¹² Tohl and Karchowski, Ber., 25, 1530 (1892).

¹² Smith and Kiess, J. Am. Chem. Soc., 61, 989 (1939)

Products of Rearrangement of 5-Ethilpperdocument and Ethilmeritlene



Pentamethylbenzene and Pentaethylbenzene. The rearrangement of pentamethylbenzenesulfonic acid ^{14, 15} is intermolecular, a methyl group being transferred from one molecule to another.

$$\begin{array}{c} \text{SO}_2\text{H} \\ \text{CH}_2 \\ \text{CH}_3 \\ \text{CH}_3 \end{array} \rightarrow \begin{array}{c} \text{CH}_3 \\ \text{CH}_2 \\ \text{CH}_3 \end{array} \rightarrow \begin{array}{c} \text{CH}_3 \\ \text{CH}_2 \\ \text{CH}_3 \end{array} + \begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \\ \text{CH}_3 \end{array} + \begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \\ \text{CH}_3 \end{array} + \begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \\ \text{CH}_3 \end{array} + \begin{array}{c} \text{CH}_3 \\ \text{SO}_2\text{H} \end{array} + \begin{array}{c} \text{30\% amorphous} \\ \text{material} \end{array}$$

Pentaethylbenzene 6, 10, 12, 16 undergoes a similar reaction, but the yields (20–30%) are inferior to those obtained in the pentamethylbenzene rearrangement. The by-products are formed in much larger quantities. This is in contrast to the tetraethylbenzenes, which rearrange more readily than the tetramethyl derivatives.

Hexamethylbenzene 2, 3 is not affected by sulfuric acid.

Octahydroanthracene. Octahydroanthracene-9-sulfonic acid ¹⁷ is rearranged by sulfuric acid to octahydrophenanthrene-9-sulfonic acid. The reaction is rapid (20 minutes at 90–100°), and yields as high as 85% have been obtained. This is one of the rare cases in which the action of sulfuric acid is improved by the presence of a diluent. Sulfuric acid containing a little acetic acid is used to effect sulfonation and rearrangement.

Halogenated Polyalkylbenzenes

4-Iodo-m-xylene.^{19, 19} When 4-iodo-m-xylene is treated with concentrated sulfuric acid and the reaction mixture is allowed to stand for several weeks the products isolated (in unspecified yields) are di- and tetra-iodoxylenes and an iodoxylenesulfonic acid.

¹⁴ Jacobsen, Ber., 20, 896 (1887).

¹¹ Smith and Lux, J. Am. Chem. Soc., 51, 2994 (1929).

¹⁵ Smith and Guss, J. Am. Chem. Soc., 62, 2634 (1940).

¹⁷ Schroeter and Götzsky, Ber., 60, 2035 (1937).

¹⁸ Hammerich, Ber., 23, 1634 (1890).

¹⁹ Tohl and Bauch, Ber., 23, 3117 (1899); 26, 1105 (1893).

$$\begin{array}{c} CH_1 \\ \hline \\ \downarrow \\ CH_2 \\ \hline \\ +1\text{Outo-e-cytiens} \end{array} \rightarrow \begin{array}{c} CH_2 \\ \hline \\ +1\text{Outo-e-cytiens} \\ \hline \\ +2\text{Outo-e-cytiens} \\ \hline$$

No rearrangements have been reported for monohalogen derivatives of oand p-xylenes.

5- (and 6-)Halopseudocumenes. The sulfonic acids of 1,2,4-trimethyl-5-chloro- and 1,2,4-trimethyl-6-chloro-benzenes rearrange to tho sulfonie acid of 1,2,4-trimethyl-3-chlorobenzene (3-chloropseudocumene) in yields of 7I and 44%, respectively. Apparently both reactions involve intramolecular migration of the halogen atom.

5-Chloropes udocumens

The corresponding 5-brome compound is converted to the sulfonic acid of 1,2,4-trimethyl-3-bromobenzene (3-bromopseudocumeno) in 90% yield. 1, 20 A small amount of 1,2.4-trimethyl-3,5,6-tribromobenzeno (tribromopseudocumene) is obtained as a by-product.

1,2,4-Trimethyl-5-iodobenzene a (5-iodopseudocumene) gives rise to two diiodopseudocumenes, an iodopseudocumenesulfonie acid, and pseudocumenc-5-sulfonic acid; the yields are not reported.

Halomesitylenes, 1, 12, 12 The sulfonic acid of chloromesitylene appears to be stable, but that of bronomesitylene rearranges easily to give a mixture of mesitylenesulfanic acid, dibromomesitylene, and tribromomesitylene. The sulfonation of iodomesitylene leads to analogous

¹⁰ Jacobsen, Ber., 22, 1550 (1989).

Kurzel, Ber., 22, 1586 (1880). 12 Tohl and lickel, Her., 28, 1000 (1491).

¹² Rose, Ann., 164, Ed (1972).

products, the character of which depends primarily on the reagent. No yields are reported.

Halotetramethylbenzenes. 12. 25. 25. All three monochlorotetramethylbenzenes 12. (1,2,4,5-tetramethyl-3-chlorobenzene, 1,2,3,5-tetramethyl-4-chlorobenzene, 1,2,3,4-tetramethyl-5-chlorobenzene) rearrange to pentamethylchlorobenzene and 1,2,4-trimethyl-3-chloro-5-benzenesulfonic acid. In these reactions migration of a methyl group must occur.

The corresponding bromo compounds, 1,2,4,5-tetramethyl-3-bromobenzene (bromodurene 21, 21), 1,2,3,5-tetramethyl-1-bromobenzene (bromoisodurene 21), and 1,2,3,1-tetramethyl-5-bromobenzene (bromoprehnitene) react differently. No migration of a methyl group occurs, but the bromine migrates intermolecularly to give dibromo compounds. The sulfonic acid from which the bromine has been removed is that of durene.

²⁴ Smith and Moyle, J. Am. Chem. Sec., 55, 1676 (1933).

[&]quot; Tohl, Ber., 25, 1527 (1892).

[™] Jacobsen, Bet., 20, 2837 (1887).

isodurene, or prehnitene, the first two of which rearrange to prehnitene sulfonic acid. The yields of dibromo derivatives are 80–100%, and those of prehnitenesulfonic acid 25-80%. The three isomeric dibromotetramethylbenzenes and bromopentamethylbenzene do not rearrange in contact with sulfuric acid, but all undergo a slow decomposition accompanied by evolution of sulfur dioxide.

9-Bromoëctahydroanthracene.³¹ The sulfonic acid of 9-bromoëctahydroanthracene rearranges when warmed with fuming sulfuric acid, hydroanthracene rearranges when warmed an octahydroanthracene sulfonic acid. The structure of the latter has not been proved; it is probably the 9-isomer.

4,6-Dihalo-m-xylene (12%) yield) when subjected to the conditions of the Jacobsen reaction.

H Koch, Ber., 23, 2314 (1508)

4,6-Dibromo-m-xylene ²⁸ rearranges in the same way, forming 2,4-dibromo-m-xylene (about 25% yield). From the behavior of other halogen compounds, it is likely that the halogen atom is the migrating group, although the same products would be produced by migration of a methyl group.

Dihalogen derivatives of o- and p-xylenes have been reported to rearrange, but the yields of definite products were very low.²⁷

5,6-Dibromopseudocumene.²⁹ 1,2,4-Trimethyl-5,6-dibromobenzene (5,6-dibromopseudocumene) was treated with chlorosulfonic acid by Jacobsen. Sulfonation was accompanied by the formation of tribromopseudocumene and 1,2,4-trimethyl-6-bromobenzene-3-sulfonic acid. The yields were not reported, but the main product isolated was tribromopseudocumene.

3- (and 6-)Halo-5-fluoropseudocumenes.³⁰ Only a few fluoro compounds have been investigated in connection with the Jacobsen reaction. No instance of migration of a fluorine atom has been reported. For example, 5-fluoropseudocumene undergoes no rearrangement when it is sulfonated and the sulfonic acid is left in contact with sulfuric acid for three months. When 3- (or 6-)bromo-5-fluoropseudocumene is treated with sulfuric acid, rearrangement involving intermolecular migration of the bromine atom occurs. The methyl groups are unaffected. The analogous chloro-5-fluoropseudocumenes give the corresponding dichloro-

fluoropseudocumene and the same fluoropseudocumenesulfonic acid; yields are not reported.

²⁸ Jacobsen, Ber., 21, 2827 (1888).

²⁹ Jacobsen, Ber., 19, 1221 (1886).

³⁰ Töhl and Müller, Ber., 26, 1108 (1893).

Halogenated Benzenes 1

The reactions of bromobenzene, p-dibromobenzene, and 1,3,5-tribromobenzene 1 with sulfuric acid have been studied. In all cases sulfur dioxide and carbon dioxide are evolved and only small yields of definite products result. Bromobenzene is converted to a dibromobenzenesulfonic acid, probably the 1,3,5-isomer; p-dibromobenzene yields 1,2,4,5-tetrabromobenzene and hexabromobenzene; 1,3,5-tribromobenzene yields hexabromobenzene.

Iodobenzene 21, 22 is converted by sulfuric acid to p-dilodobenzene and benzenesulfonie acid, with hiberation of some iodine and hydriodic acid. o- and p-Iodotoluenes undergo a similar reaction. p-Diiodobenzene and fuming sulfuric acid give a mixture of tri- and tetraiodobenzenes;" experimental details are lacking.

It is quite obvious that the Jacobsen reaction as applied to halogenated benzenes to form polyhalogenated benzenes is not one of practical synthetic value.

There appear in the literature 24 some rearrangements of 1,8-dichloronaphthalene which resemble the Jacobsen rearrangement. When 1,8dichloronaphthalene is heated with hydrochloric acid at 200, a rearrangement to 1,5-dicbloronaphthalene occurs. A similar conversion also results from the action of sulfuric acid, but considerable decumposition occurs simultaneously. Heating with phosphoric acid or in the absence of any acid fails to bring about a rearrangement of the dichlorus naphthalene. Only the 1,8-dichloro isomer undergoes rearrangement. The 1,8-dichloro-inaphthalenesullonic acid is hydrolyrod by acid at 230° to give 1,8-dichloronaphthalene; the 1,8-dichloros3-naphthalene sulfonic acid, however, undergoes hydrolysis only if a temperature of 285° is reached, and then a mixture of the 1.85, the 1.55 and the 1.75 dichloro derivatives results.

EXPERIMENTAL PROCEDURES

1,2.3,4-Tetramethylbenzene (Prehnltene)

From Pentamethylbenrene." To 74 g of pentamethylbenrene (m.p. 52°) heated to 65°, 200 g of concentrated sulfuric acid is added (m.p. 02) neutra to 65, 500 to concentrate saturae and is added and the mixture is shaken vigorously. This procedure results in a much and the mixture is smaken againetis). And procedure results in a much of fine crystals of the hydrocarbon in the sulfuric acid; lumps must be

in Cass, Ph.D. thesis, University of Minnesots, 1931. 11 Neumann, Ann., 241, 33 (1987).

¹³ Boyle, J. Chem. Soc. 95, 1683 (1909). Marmetrong and Wynne, Chem. News, Ts, 69 (1897).

avoided; if any are formed they should be broken up. The reaction mixture of crystals and red liquid is allowed to stand at room temperature for twenty-four hours, then cooled in an iee-salt bath. To it is now added 165-200 g. of eracked iee in three portions with vigorous stirring. The cold mixture is filtered and the filter cake pressed as dry as possible; the precipitate is then stirred with 700 ec. of cold water and again filtered. The product is a mixture of hexamethylbenzene and tar while the red aqueous filtrate contains the prehnitenesulfonic acid.

The filtrate is treated with excess of powdered calcium carbonate, and the precipitated calcium sulfate is filtered and thoroughly washed with water. The calcium prehnitenesulfonate in the combined filtrate and washings is converted to the corresponding sodium salt by addition of a saturated aqueous sodium carbonate solution as long as any precipitate forms. The precipitated calcium earbonate is filtered and washed with water. The filtrate and washings are evaporated to dryness on the steam bath. The residue of sodium prehnitenesulfonate weighs 40 g.

Since the prehnitenesulfonic acid undergoes extensive decomposition when heated with sulfuric acid, the sodium salt is advantageously hydrolyzed to the hydrocarbon by a "flash" method. In a steam-distillation flask, provided with openings for a thermometer and dropping funnel, is placed about 100 ee. of water. Superheated steam is passed into the flask, and concentrated sulfuric acid is then added slowly from the dropping funnel until the temperature of the diluted acid reaches 150-160°. At this point a saturated aqueous solution of 40 g. of sodium prehnitenesulfonate or a thin paste of solid and water is run into the flask at such a rate that the temperature of the mixture remains at 140-150°. Careful control of this temperature is essential. Hydrolysis takes place rapidly, and a pale yellow oil separates from the distillate. The crude oil weighs 20 g. (88%). Upon distillation, over 90% boils at 97-98°/24-25 mm.; m.p. -7.4°. Highly purified prehnitene melts at -6.4°.

From a Mixture of the 1,2,4,5- and 1,2,3,5-Tetramethylbenzenes (Durene and Isodurene). A mixture of durene and isodurene, b.p. 82-84°/15 mm. can be obtained by fractionation of the hydrocarbons produced by the reaction of methyl chloride and aluminum chloride with the mixed xylenes (see ref. 3 for details). A mixture of 100 g. of this fraction, 67 cc. of concentrated sulfuric acid and 33 cc. of 60% fuming sulfuric acid is shaken (in a 500-cc. glass-stoppered Erlenmeyer flask) for about five minutes. The resulting solution is heated to 80° for a period of nine hours. The black, nearly solid reaction mixture is then broken up and poured over 500 g. of crushed ice. After filtration of the insoluble material (18 g.) the solution is cooled to ÷10° and the sul-

65-70° for four hours and is then poured over 150 g. of crushed ice. The resulting mixture is cooled in a salt-ice bath until crystallization of the sulfonic acid of 3-chloropseudocumene is complete. The cold mixture is then filtered and the cake is pressed dry. The sulfonic acid is dissolved in 75-125 cc. of water, and the insoluble tar (4.5 g.) is filtered and discarded. The cold solution is treated with an excess of 20% sodium hydroxide, and the precipitate of sodium sulfonate is collected by filtration. The filtrate is concentrated to one-third volume, chilled, and filtered to yield a second crop. The total yield of sodium 3-chloropseudocumenesulfonate, after drying at 110°, is 35.4 g. (71%).

The sodium salt is dissolved in 250 cc. of 50% sulfuric acid, in a 500-cc. flask arranged for steam distillation. The flask is heated in an oil bath until the internal temperature is 135-155°. Steam is passed into the liquid until the distillate is homogeneous. The organic layer of the distillate is separated, dried over a little calcium chloride, and distilled under diminished pressure. The pure 3-chloropseudocumene, boiling at 127°/61 mm., weighs 17.2 g. (79%, based on the sulfonate).

3-Bromopseudocumene. By vigorous shaking, 19.9 g. of crude 5-bromopseudocumene is dissolved in 120 g. of 20% fuming sulfuric acid which is maintained at 70°. After solution is complete the reaction mixture is treated as described in the above procedure. The sodium salt of 3-bromopseudocumenesulfonic acid, which weighs 27.1 g. (90%), is hydrolyzed by steam distillation from 50% sulfuric acid maintained at 175°. The 3-bromopseudocumene boils at 85.5–86.5°/5 mm. and weighs 14.5 g. (80%, based on the sulfonate).

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